VOLUME 59 • MARCH 1958 • NUMBER 3

OPHTHALMOLOGY

Some Modern Concepts of Ocular Wound Healing
John H. Dunnington

Accommodation-Convergence Association
Fred C. Sabin and Kenneth N. Ogle

Studies on Simulated Vitreous Hemorrhages
H. Karl Boyer, Anita A. Suran, M. J. Hogan, and W. K. McEwen

Agenesis of the Medial Rectus Muscle
Louis J. Girard and Robert A. Neely

Human Amnion-Cell Tissue Culture
Herbert E. Kaufman and Eleanor Kaufman

Acute Suppurative Dacryoadenitis as a Sequel to Mumps
Narendra Krishna and Wood Lyda

Electronic Pupillography
Otto Lowenstein and Irene E. Loewenfeld

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Marshall M. Parks

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Guillermo Picó

The Surgery of Cataract in Megalocornea
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II. Effects of Oxygen Tension

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Congenital Paralysis of Lateral Conjugate Gaze
S. H. Witzel

An Effective Portable Animal Platform for Zeiss Opton Slit Lamp Examinations
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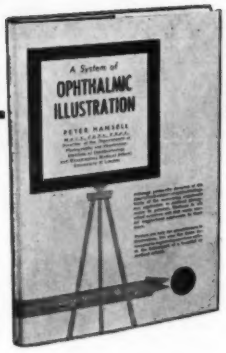

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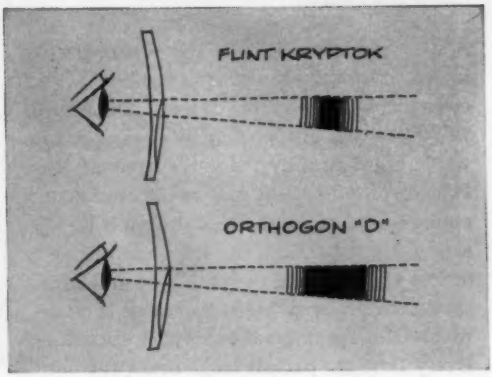

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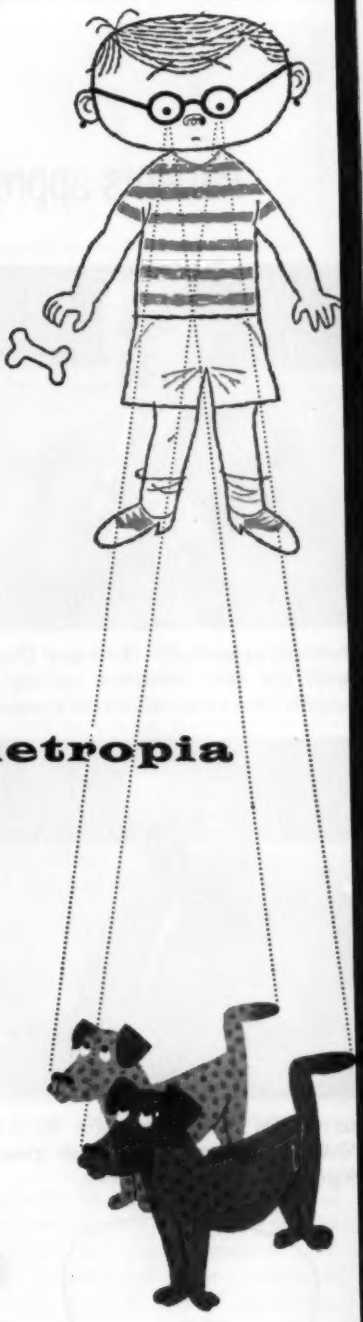

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Correct base curves are also very important because they can change the size of the retinal images. The size of the retinal image depends on the correction, of course, but also on the distance from the nodal or principal point of the eye to the nodal point of the lens. In a plus lens as this distance increases the image size becomes larger and in a minus lens the image size becomes smaller.

The position of the nodal point of any ophthalmic lens depends upon its curvature. It is upon this fact that the lenses to correct unequal retinal images are based.

The above facts are presented because they have a bearing on the case of Mr. S. which we present now. Mr. S. required a +1.50 sphere in each eye combined with a small cylinder. The correction had been worn comfortably for years. One lens was broken and replaced and Mr. S. immediately started having eye trouble.

He reported back to his oculist who checked the new lens for power, axis, position of the optical centers, etc., and found everything as it should be. The oculist then checked the base curve of the new lens and found it very different from the curve of the old lens. A new lens was ordered with the same base curve as the old lens and the patient's symptoms disappeared.

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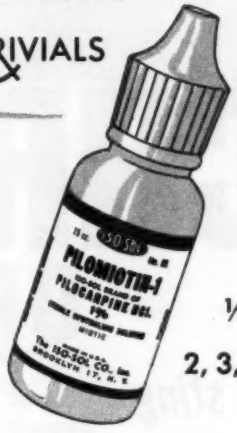

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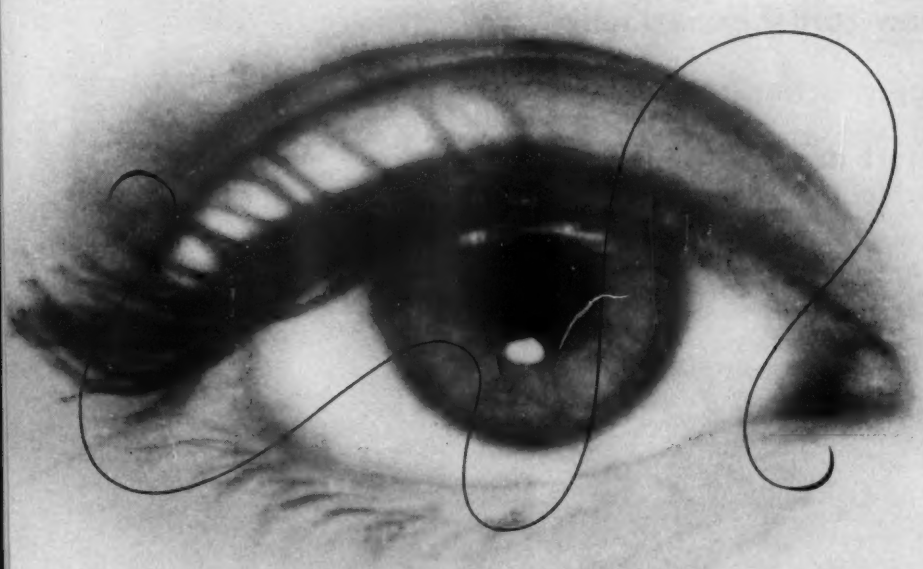

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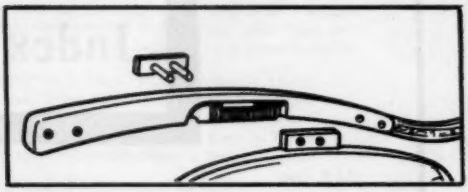

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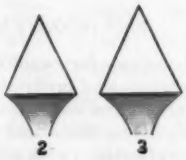

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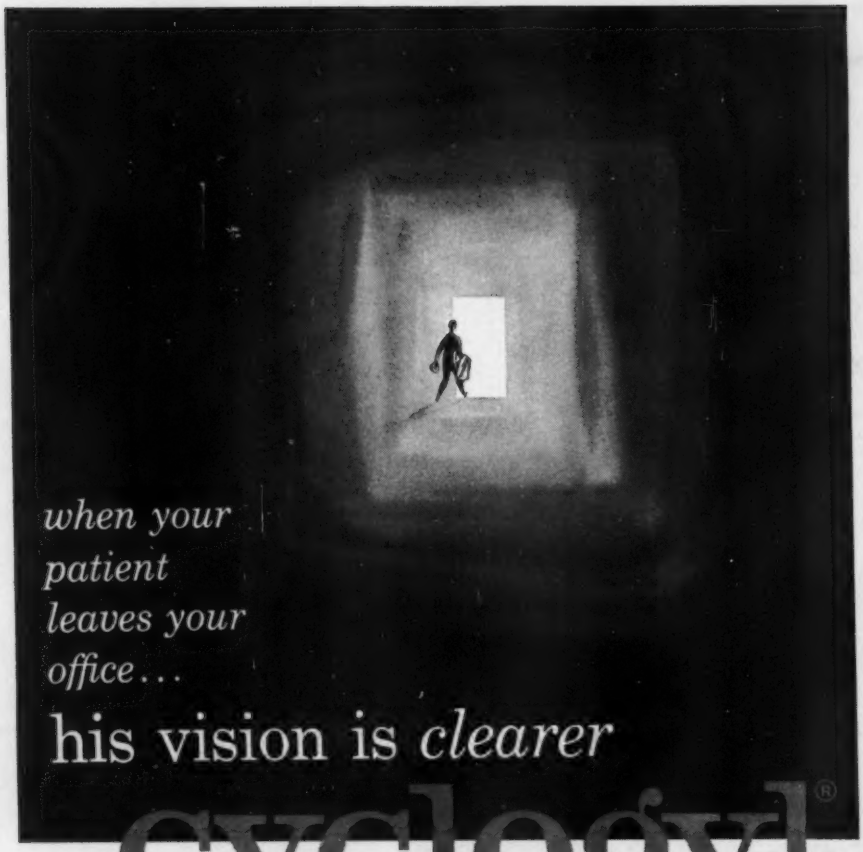

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A.M.A. ARCHIVES OF
OPHTHALMOLOGY

Some Modern Concepts of Ocular Wound Healing

The Twentieth Lecture in Honor of George Edmund de Schweinitz, M.D.

JOHN H. DUNNINGTON, M.D., New York
With the assistance of Ellen F. Regan, M.D.

It is both a pleasure and a privilege to present this lecture in memory of Dr. George Edmund de Schweinitz. His manifold contributions to American medicine are well known, for he was not only an outstanding ophthalmologist but also an executive of rare ability. His keen clinical judgment, his concise scientific contributions, and his great integrity won for him the highest honors in American ophthalmology. In recognition of his valuable services during World War I he was appointed consultant in Ophthalmology to the United States Army. He served as President of the American Medical Association—an honor richly deserved because of his qualities of great leadership, lucidity of thought, and clarity of speech. In addition to the tributes he received in this country, he was the first American to deliver the Bowman Lecture, sponsored by the Ophthalmological Society of the United Kingdom. To have known this delightful gentleman and distinguished physician is one of my most cherished memories, and so I welcome this opportunity to express my personal esteem of him and to pay homage to his name.

For several years we, at the Institute of Ophthalmology, have been especially interested in ocular wound healing. Both the experimental and the clinical aspects of the problem have been attacked by a corps of scientists and clinicians. Tonight I shall present the results of these studies and attempt to correlate the experimental findings with clinical observations. To do it, let us consider the structures involved and their relation to some of the clinical manifestations of imperfect healing.

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Epithelium

Although many new concepts of healing have been evolved, our understanding of the reactions of epithelium dates to 1896, when Ranvier, studying the healing of abrasions of the rabbit cornea, demonstrated the importance of the mechanical slide of adjacent epithelial cells in covering a denuded area.[1] This process, beginning within an hour after injury, progresses rapidly and only later is reinforced by active mitosis in the surrounding epithelial cells. The spread continues until the surface is covered or until epithelium reaches epithelium. In covering the surface of a wound epithelium does not bridge any gap in continuity but lines every crevice of the defect. When the lining has been completed, the epithelium proliferates to fill out the depression. As healing progresses, the epithelial plug is gradually pushed to the surface by the increasing participation of the stromal ele-

ments. Another characteristic of epithelium, recognized for many years, is the facility with which it grows along any smooth surface, e. g., nonabsorbable surgical (silk) sutures, lens capsule, or a fibrin strand. Recently Gillman and Penn, studying the healing of skin wounds in rabbits and humans, demonstrated that epithelial proliferation along the suture track and within the wound edges continues until the advancing cells meet.[2] In our investigations of the healing of cataract incisions in monkeys, we have seen similar epithelial spread along silk corneoscleral sutures.[3,4] In many instances the growth is so rapid that the entire suture track becomes lined by cells in two to four days, which is before fibroblasts are present in good number along the wound lips. Such epithelial cords usually lose their continuity with surface epithelium, and clumps of these cells many remain isolated in the stroma.

Howes has stated that healing will not occur until epithelial surfaces meet.[5] Recently we have tried to establish the veracity of this statement. For this study, which will later be reported in detail, the experimental animals were rats. After they were anesthetized with ether, the corneal epithelium was first loosened by instillation of cocaine drops (4% solution) and then removed with a cotton swab. With a von Graefe knife, a 5 mm. penetrating incision was made through the middle of the cornea. In some eyes the epithelium was denuded daily to prevent it from spreading into the area of the wound, while in others the epithelium was removed only at the time of operation. The animals were killed at intervals from 4 to 96 hours after operation, and the eyes were enucleated and fixed in formalin-alcohol solution. They were then prepared and stained with Giemsa stain, with use of the technique described by Weimar.[6] Cell counts were carried out on whole mounts of corneal stroma. When epithelium was not permitted to grow into the incision, the number of corneal fibroblasts in the healing wound at 48 hours was less than 25% of the normal number. In those eyes in which the epithelium, after being denuded from the cornea, was permitted to grow back into the incised area, the number of corneal fibroblasts was decreased by only 50%. This finding suggests that epithelium has a stimulating effect upon the healing of a corneal incision.

Clinically the tendency of epithelium to invade all crevices along the surface of an incision is manifest in the deep furrow seen after a corneal suture and in epithelization of the anterior chamber. Whereas the former finding is not an important complication, any form of epithelial invasion of the anterior chamber is serious. From our experimental studies of ocular healing, we agree with Theobald and Haas that epithelium may gain access to the anterior chamber by the following routes: (1) implanation of free conjunctiva or cornea, (2) inturning of a conjunctival flap, or (3) ingrowth of epithelial cells along a gaping wound, incarcerated tissue, or a deeply inserted suture.[4,7]

From the time of Masse (1880-1881) to the present there have been reports of growth of epithelium within the anterior chamber after the experimental implantation of conjunctival or corneal epithelium.[8-10] Such lesions usually had the appearance of epithelial cysts, and their growth depended upon the establishment of nutritive support from the iris. When we placed a free piece of conjunctiva on the surface of the iris of monkey eyes, epithelial growth was first evidenced by a fine membrane on the iris surface around the implanted tissue. Sometimes the epithelial cells continued to spread and lined the angle of the anterior chamber and extended onto the posterior corneal surface. In other instances the cells invaded the iris crypt and formed small epithelium-lined cysts. These findings are similar to those reported by Cogan on the growth of free conjunctival epithelium in the eyes of rabbits.[10] We have found that epithelium may grow into the anterior chamber along incarcerated tissue unless the inflammatory

reaction in the vicinity of the wound is sufficiently great to destroy the invading epithelial cells or unless the proliferation of fibroblastic tissue is excessive.[4] It was also noted that epithelial cells extended along deep silk sutures into the posterior part of the incision but did not invade the anterior chamber unless the iris was caught on the suture. In these instances the invasion occurred whether the incision was corneal or limbal with a conjunctival flap. However, when the suture material was mildly chromicized 000000 absorbable surgical (gut) sutures no such epithelial ingrowths were observed. Thus, we may theorize that although the smooth surface of silk facilitates the growth of epithelium its invasion of the anterior chamber is largely dependent upon the nutrient supporting base provided by the iris.

The tendency for epithelium to line all crevices and the nutritive support provided by the iris shed light on the later appearance of epithelization in the presence of intermittent fistulization of the wound. When this condition exists, intermittent wound breaks permit the epithelial cells to spread into crevices and eventually line the wound edge. As the track continues to reopen, it becomes more and more lined with epithelial cells until eventually they reach iris tissue and establish a firm nutritive base. Therefore, to avoid invasion of the anterior chamber, all fistulizing wounds should be closed promptly. Cauterization alone is inadequate, and valuable time may be lost by using the so-called conservative measures. It is our belief that in all fistulas gentle cauterization and careful curettement of the track should be done before the opening is resutured and covered with a conjunctival flap.[11,12]

We agree with Calhoun that the type of epithelial growth depends on whether the cells become embedded in an iris crypt or find support on the surface of the iris.[13] In the former instance, one can imagine epithelial cells spreading to line a crypt, thus forming a cyst which will enlarge slowly because of the pressure exerted by the surrounding iris. Should epithelium find its nutrient base of the surface of the iris, it is easy to visualize its spread along the surface of the iris and on the posterior aspect of the cornea. This spread will be rapider because the cells are not confined by the surrounding stroma. It will be indefinite because of the tendency of epithelial cells to spread until they encounter other epithelial cells. Even the knob-like protuberances so characteristic of the advancing corneal border of an epithelization are not unlike those seen when epithelium in vitro extends over smooth surfaces.

These characteristics of epithelium explain many of our clinical observations. We know that epithelial cysts of the iris or anterior chamber occur more frequently after perforating injury or needling operations, while epithelization is usually seen after a larger limbal incision, with or without a conjunctival flap. In the former there is often a considerable and sudden force associated with the introduction of epithelium into the anterior chamber, and this force might be sufficient to embed epithelial cells within the iris crypts. In the latter group, epithelium is continuous with the surface cells and spreads along a smooth pathway onto the surface of structures lining the anterior chamber.

With our present knowledge of the pathogenesis of epithelial invasion of the anterior chamber, we may speculate upon the treatment of epithelization of the anterior chamber. More recent studies have led us to question the efficacy of roentgen therapy for this condition. Theoretically, any successful treatment should destroy the epithelium within the chamber as well as remove its source of nutrition. Many of the techniques for treating epithelial or posttraumatic cysts aim only at destroying the epithelial lining of the cyst. Diathermy and chemical cautery can accomplish such destruction in cystic lesions, but their use in epithelization of the anterior chamber is contraindicated because of the diffuseness

of the lesion. Long and Tyner and Maumenee and Shannon treated epithelial invasion by first applying alcohol to the posterior surface of the cornea and then curetting off the epithelium. More recently this procedure has been combined with a broad iridectomy.[14,15] The latter step is, in all probability, the most important one, because a broad iridectomy may arrest the growth of epithelium by depriving it of its nutritive support.

Bowman's membrane, possessing no power of regeneration, plays a relatively unimportant role in the reparative process. When it is incised, the cut ends may retract, allowing epithelium to come in direct contact with the stroma, or they may become snarled in the contracting scar. Epithelial disturbances do occur as late manifestations of extensive damage to this structure.

Stroma

Tissue responses of the corneal stroma involve both cellular reactions and alterations in the fibers and ground substances. We know that a chemotactic substance (a polypeptide) liberated by the injured cells sets in motion a complex chain of events which leads to the appearance of polymorphonuclear leukocytes, the activation of proteolytic enzymes, and the arrival of lymphocytes, macrophages, and fibroblasts in the injured area.[16-18]

Weimar has made some pertinent observations on the cellular responses to a corneal injury.[6,19,20] From her studies on the healing of corneal incisions on rats, she demonstrated that the machinery of repair is already in motion by the second postoperative hour. She noted that during the fourth hour after operation polymorphonuclear cells normally invade the wound edges. Furthermore, this response can be inhibited by applying either sodium salicylate or soybean trypsin inhibitor to the incision during the second hour after operation. More recently, using whole mount preparations of the corneas of rats on which a perforating incision had been made, she observed that corneal fibroblasts arise first from transformation of the stromal cells of the cornea in the immediate vicinity of the incision and later from monocytes which have migrated to the injured area. Throughout these experiments she was unable to demonstrate the presence of mast cells within the corneal stroma, even though they were plentiful in the connective tissue at the limbus.

In the cornea these cellular responses to injury are either preceded or accompanied by characteristic changes in its ground substance. Our methods of investigating such changes include not only histochemical studies but also the use of radioautographs. Dunnington and Smelser have studied the incorporation of S^{35} in healing wounds in normal and devitalized corneas.[21] They found that the ground substance is the earliest new connective tissue element present in a healing wound. Radioautographs made 24 to 48 hours after operation indicate synthesis of sulfated mucopolysaccharides in a narrow cellular band on the wound edge. This reaction occurs before metachromasia can be demonstrated by histochemical techniques. In devitalized corneas the processes of healing were greatly delayed. When the stromal cells in the wounded area were destroyed, the ground substance was not replaced at a normal rate until a considerable length of time had elapsed after the cells had been restored.

We have reported on the alterations in mucopolysaccharides during the healing of limbal incisions in monkeys.[22] We demonstrated by the toluidine blue method of differential staining that activation of the mucopolysaccharides becomes apparent on the third postoperative day in the form of small aggregations of a purple-staining substance around the blood vessels of the subconjunctival tissue. By the fifth day after operation, fire red granules similar to those described by Sylvan in skin wounds were present in the corneal stroma near the wound edges.[17] On the seventh day metachromasia occurred around the large

mononuclear cells which filled the anterior half of the wound. By the 10th to 14th day, metachromatic changes, which had extended to the posterior part of the incision, had decreased in the immediate edges of the anterior part of the wound.

In these studies on the healing of limbal wounds in monkeys, we also investigated the behavior of the fibers during the reparative process. To demonstrate reticulin we used Wilder's silver carbonate staining technique. By this method only very few fibers were visible at the end of three days after operation, but their number increased rapidly during the next four days. They were found to accumulate not at the wound edge but at sites slightly away from it, where fibroblasts or large mononuclear cells were present. In the course of the second postoperative week the reticulin fibers decreased in number, appearing and disappearing last in the posterior part of the incision.

The appearance of collagen, as demonstrated by van Gieson's method, paralleled the decrease in reticulin fibers. On or about the fifth postoperative day, traces of immature collagen appeared around the blood vessels in the subconjunctival tissue. By the seventh day collagen was present in varying amounts in all eyes, and by the 10th or 11th postoperative day there was new collagen formation throughout the wound. During the next two or three weeks the collagen in the anterior part of the incision slowly matured, but not until the end of four weeks was there any sign of maturation of collagen in the posterior part of the wound.

As has been demonstrated, both in pathological examinations and in experimental studies, limbal and corneal wounds first show signs of healing anteriorly. In the presence of a limbal incision with a conjunctival flap the initial changes take place around the episcleral vessels, but if the incision is corneal the changes occur beneath the epithelium. The reason for this delay in healing of the posterior part of these incisions is not clear. Does the aqueous humor exert a retarding effect? Although its exact role has not been determined, there is considerable evidence that the aqueous humor, per se, is not a good nutrient medium.[23] From tissue culture studies and from attempts at tissue growth in the anterior chamber, it has been learned that cells may remain viable in aqueous humor but do not give evidence of extension or mitosis until further nutrition is derived from the blood vessels of the iris or other tissues.[23,24]

Abnormalities in stromal growth may assume different forms. The simplest one is the formation of a broad band of fibrous tissue between the lips of the incision. This condition results from poor apposition of the wound surfaces, which can be produced by overriding of the edges of the incision, by incarceration of tissue, and by repeated small ruptures of the wound. We have produced, experimentally, broad cicatrices by all the foregoing methods and have studied the histological characteristics of such wounds. From these investigations it can be stated that collagen fibers in wide scars, though numerous, never reach the maturity of those in normal tissue. Therefore, these wounds are weak, because the rise in tensile strength of any wound parallels the rise in and maturity of its collagen fibers rather than the appearance of fibroblasts.[25] As clinicians we are all familiar with the frequent development of a staphyloma in an eye with a broad cicatrix and also the ease with which these wounds rupture.

The corneal stroma sometimes exhibits a property called, by Duke-Elder, "stromal overgrowth."[26] This proliferation was described by Henderson, in 1914, and later by Collins, Swan, Levkoieva, and Tikhomirov.[27-30] Although there have been several theories about the cause of this exuberant growth of stromal tissue, the milieu in which it will develop has definite characteristics. First, the wound edges are in poor apposition. Second, there is an irritating stimulant within the eye. Third, vitreous, lens matter, or iris is incarcerated within the

wound. When the surfaces of the wound are in poor apposition, the cut ends of endothelium and Descemet's membrane separate, and the proliferating stromal tissue may thus gain entrance to the interior of the eye. The second and third influences are doubtless closely interrelated, for the incarcerated lens matter, vitreous, or iris tissue often causes an iridocyclitis, which in turn leads to a protein-rich aqueous humor that acts as a more nutritive medium for cell growth. However, incarcerated tissue may serve as a pathway down which the fibrous tissue can grow into the anterior chamber.

In an attempt to establish the effect of vitreous loss upon stromal overgrowth, 24 monkey eyes were operated upon. The monkeys were anesthetized with intravenous pentobarbital, and the operation was performed with use of the standard surgical procedure reported in earlier experiments.[3] In addition, the hyaloid membrane was ruptured with an iris spatula and vitreous was allowed to herniate between the lips of the incision before the corneoscleral sutures were tied. The animals were killed at frequent intervals; the appearance of the eyes was recorded before they were fixed in a preparation of pyroxylin (Celloidin), sectioned serially, and stained with hematoxylin and eosin.

The reactions were minimal in those eyes in which several well-approximated corneoscleral sutures had been used to close the incision. These wounds were broader than normal, and the iris pillars were incarcerated between the posterior edges of the incision, but there was no excessive cellular reaction, and the incisions were firmly closed. In the absence of supplementary corneoscleral sutures there was a large area of posterior gaping filled with round cells, probably fibroblasts or their precursors. Sometimes these cells were confined to the posterior part of the incision, but oftener they extended in strands into the anterior chamber. Stromal overgrowth was seldom prominent until three to six weeks after operation, and it was more excessive when the lens was injured.

Such stromal overgrowth is not necessarily confined to instances of vitreous loss or incarceration of lens matter. Offret and others have observed a retrocorneal membrane of fibrous tissue on the back of an unsuccessful corneal graft.[32,33] Offret states that these membranes arise from either host or graft cornea at the edge of the section and are prone to occur "when the section of the pathological cornea is irregular." He considers the persistence of debris from Descemet's membrane important to the development of this fibrous tissue membrane. We have seen similar exuberant growths of fibroblastic tissue in poorly apposed penetrating corneal incisions made on the eyes of cats and rabbits. In many instances the "stromal overgrowth" extended both over the back of the cornea and into the anterior chamber.

Endothelium

When we turn our attention to Descemet's membrane and the endothelium, we discover that their role in healing is not as firmly established as that of the other corneal tissues. It is well known that if Descemet's membrane is cut the ends retract, curl forward, and make no attempt to unite. However, in contrast to the lack of reformation of Bowman's membrane, we know that a new Descemet's membrane is produced by proliferating endothelial cells. Weinstein found active mitosis and new endothelial cells massed at the cut edges of Descemet's membrane on the second postoperative day, and by the third day endothelial cells had spread over the posterior surface of the incision.[1] As pointed out by Stocker, the endothelial cells are highly vulnerable.[34] He cites Nagano, whose investigations showed that even an epithelial abrasion led to changes in the arrangement of the endothelial nuclei.[35] Furthermore, his own studies have revealed that proliferating endothelial cells are often very different from normal endothelial cells. He found that after the endothelium was injured with a

needle prick the defect became covered by cell spread or slide. The phenomenon began about 20 hours after injury and was complete at the end of the 4th day. The cells, however, lacked the pattern of normal endothelial cells. Binder and Binder have made similar observations. In their experiments they scraped the endothelium from rabbit corneas and from the beginning found a large number of endothelial cells with enlarged nucleoli and a delicate nuclear membrane.[36] At the end of 12 hours the cells showed both mitotic and amitotic division. The mitosis was very active from 24 to 36 hours after injury and then decreased rapidly, until none was evident on the 5th day. The wounds were covered by endothelial cells on the fourth day.

Studying our slides of monkey eyes, Stocker found no proliferation of endothelium four days after operation, and the area between the curled ends of Descemet's membrane was covered with a single layer of attenuated cells which did not entirely resemble endothelial cells.[34] These cells were sometimes found unconnected with normal endothelium, but their appearance was slowly transformed into that of endothelial cells. Stocker has suggested that these cells arise from corneal fibroblasts. In our studies on the healing of the posterior part of a limbal incision, we found considerable variation in appearance of the endothelium. When the posterior edges of the incision were in close apposition, endothelial or endothelial-like cells had covered the area at the end of the fifth postoperative day. When there was posterior gaping without tissue incarceration, the endothelial cells were elongated and attenuated in the area of the incision and seemed to spread in a single line along the edge of the lips of the incision. Often the posterior triangle was filled with cells which resembled fibroblasts and at the edge of the incision formed a layer of attenuated cells parallel with the cells of the endothelial layer. These cells, which in many respects resembled those of the endothelium, were always in continuity with corneal fibroblasts but not necessarily with endothelial cells. Thus, it would appear that the proliferating endothelial cells do arise, at least in part, from fibroblasts.

There are many facets of endothelial healing and of the reproduction of Descemet's membrane which are unsolved, but appreciation of the high vulnerability of the endothelium is of clinical importance. Recognizing this fact, all surgeons zealously guard against trauma to the posterior part of the incision and, if possible, avoid operating in the presence of endothelial disease. Furthermore, many measures have been suggested to minimize trauma to the cornea, and yet little emphasis has been placed upon the role that accurate apposition of the deeper layers of the incision plays in the prevention of these complications.

Summary

Although the complex problems of wound repair are far from solved, some progress has been made. In this discussion on the role of the various tissue components in the healing of corneal and limbal incisions, attention is directed to both the normal and abnormal responses. Epithelium, which has as its characteristics rapidity of growth, tendency to line all crevices, and progression until it meets another epithelial surface, accounts for early covering of surface wounds; however, under abnormal conditions these same properties may be responsible for clinical complications. With this in mind, consideration is given to the pathogenesis of epithelial invasion of the anterior chamber.

Reactions of the corneal stroma are also reviewed, with emphasis on the more recent investigations of both cellular and noncellular components. These changes have been demonstrated by radioautographs and by whole-mount preparations of corneal stroma. Abnormalities of stromal healing are manifest by broad scars and stromal overgrowth. The conditions responsible for these deflections are discussed.

The role of Descemet's membrane and of endothelium is not clear, but there is evidence that endothelial healing takes place by the transformation of proliferating corneal fibroblasts.

Dr. George K. Smelser and Dr. Virginia Weimar gave permission to discuss their investigations.

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Accommodation-Convergence Association

Experiments with Phenylephrine, Pilocarpine, and Physostigmine

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Introduction

In a recently published paper [1] data were described which showed that the amount of convergence associated with a given change in the dioptric stimulus to accommodation is greatly increased when the eyes are under cycloplegia induced by homatropine over that when they are in the normal state. This phenomenon was first described by Maddox and more recently by Morgan.[2] As measured quantitatively, homatropine causes a marked increase in the accommodative convergence-accommodation (stimulus) ratio [(A−C)/A] over that ratio measured normally. The increase seems to vary as a function of the degree of cycloplegia. The data were obtained by the fixation-disparity technique. With this technique of measuring ocular-motor imbalance, extrafoveal binocular vision and fusion are maintained throughout the test and both eyes are subjected simultaneously to the same dioptric stimulus to accommodation. Most interestingly, the data showed that in the presence of homatropine cycloplegia the change in the accommodative convergence was proportional to the change in the stimulus to accommodation, throughout the range of response to that change, regardless of the increased value of the (A−C)/A ratio. That is, the ratio of the accommodative convergence-accommodation stimulus remains constant but at a higher value than that found normally. It was found also that the homatropine did not, in general, affect the pattern of ocular motor imbalance when the eyes were forced to converge or diverge with prisms at a fixed observation distance.

The data showing this marked increase in the (A−C)/A ratio with homatropine in young, nonpresbyopic eyes were compared with similar data obtained for completely presbyopic subjects. For the latter group the (A−C)/A ratios seemed to fall within the normal range of the population in general. It was concluded that the visual and ocular-motor processes involved in the two instances were different, although as yet the reason for this difference is not clear.

When the eyes are under the influence of homatropine, the range of actual accommodation is greatly reduced, but there is still an accommodative convergence response to changes in the stimulus to accommodation, unless that change is too large. At the same time, of course, the pupils are dilated, and one must consider the possible influence of the large pupil itself on the (A−C)/A ratio. If the "retinal stimulus" to accommodation is somehow related directly to the blur of the retinal image, then a greater blur and therefore a greater stimulus to accommodation would be caused by a given actual dioptric change in stimulus to accommodation with a larger pupil than would be caused by the same change when the pupil was smaller. This follows because the depth of focus is greater with a smaller pupil than with a larger one.

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This paper is concerned with studies of the accommodation-convergence relationship (1) when the pupil is enlarged by phenylephrine (Neo-Synephrine) with little or no effect on the ciliary muscles and (2) when the pupil is made smaller owing to the ciliary body and iris being under the influence of pilocarpine or physostigmine (Eserine). The fixation-disparity technique was again used to obtain a measure of the ocular-motor imbalance when the normal relationship between accommodation and convergence is systematically changed, first, by prisms and, second, by ophthalmic lenses. From the two sets of data obtained, the relationship between the two functions could be derived.

Instrumentation

A detailed description of the instrument used for these measurements will not be given here, and the reader is referred to previous papers.[1,3] Experiment has shown that if an ocular-motor imbalance (lateral phoria) exists, in spite of the absence of diplopia, a lateral disparity between the images of all object points on the test target can be measured by a suitable apparatus. This disparity (fixation disparity) is in the direction of the phoria and indicates an overconvergence in the case of esophoria and an underconvergence in the case of exophoria. The magnitude of this disparity is always small, measurable in minutes of arc, and it depends on the amount of detail for fusion present in the test field, the degree of phoria, and probably the strength of the compulsion-to-fusion reflex.

Procedure

The tests were made at a near observation distance of 33 cm., with the subject's head held before a phorometer.

Two different sets of data were obtained. First, the fixation disparity was measured when convergence or divergence was forced by the prismatic deviation produced by calibrated rotary prisms before the eyes. Second,

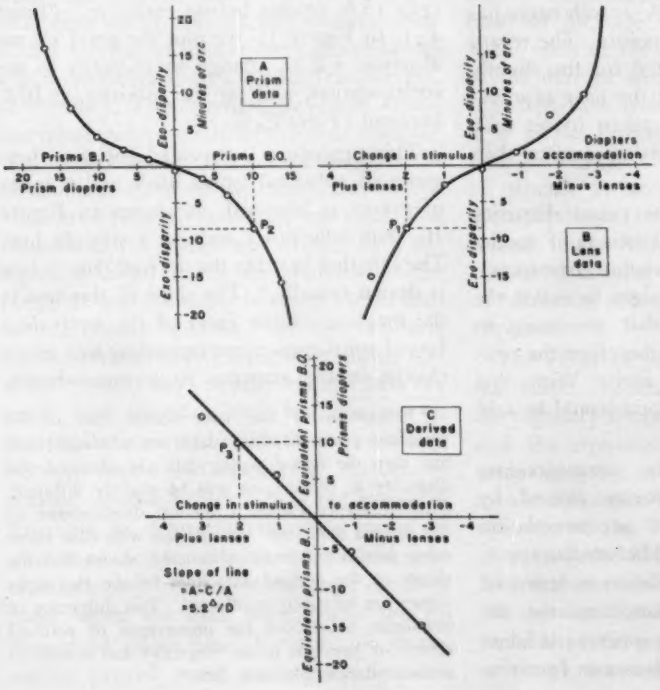

Fig. 1.—Typical curves of the fixation-disparity measurements. *A*, the prism-disparity curve; *B*, the lens-disparity curve; *C*, the derived curve. The slope of the best-fitting line is equal to the (A—C)/A ratio.

the fixation disparity was measured when the stimulus to accommodation was changed by placing spherical ophthalmic lenses before the eyes. These data, when plotted, resulted in curves characteristic of the subject's particular ocular-motor behavior under the conditions of the test. Under the same test conditions the results are reproducible.

Typical curves for the normal state of the eyes are shown in Figure 1*A* and *B*. Figure 1*A* shows the change in ocular-motor imbalance, as measured by the fixation disparity, when convergence is forced by prisms, with a fixed observation distance and therefore with a constant stimulus to accommodation. On the abscissa is the amount of forced convergence (positive) or divergence (negative) in prism diopters indicated by the rotary prism, base-out and base-in, respectively. The measured fixation disparity in minutes of arc is plotted on the ordinate: eso-disparity (overconvergence in the sense of an esophoria) positive, and exo-disparity (underconvergence in the sense of an exophoria) negative. A smooth curve has been drawn through the points. The rotary prism setting was corrected for the slightly decreased effectiveness at the near observation distance. Care was taken to set each of the units with a precision greater than 0.5Δ.

The point at which the prism disparity curve crosses the abscissal axis is of special interest. The prismatic deviation corresponding to this point, which might be called the "equivalent phoria," is that necessary to reduce the disparity, and therefore the ocular-motor imbalance, to zero. With this prismatic deviation the phoria would be said to be corrected.

Figure 1*B* shows the corresponding changes in fixation disparity caused by changing the stimulus to accommodation (ophthalmic spheres placed before the eyes). The stimulus to accommodation in terms of diopters of spheres is plotted on the abscissa. An increase (minus spheres) is taken positive to the right, a decrease (positive spheres) is taken negative to the left. The true stimulus to accommodation for each sphere used must be determined from the dioptric position of the image of the test target as seen through the lens. Hence, a small correction factor must be applied. The ordinate is the same as in Figure 1*A*.

The desired data relating the change in stimulus to accommodation to the accommodative convergence are derived from the Curves 1*A* and 1*B*, as shown in Figure 1*C*. In this graph the abscissa is again the change in the stimulus to accommodation, but on the ordinate is plotted the equivalent prism convergence (or divergence) that will cause the same disparity as does a given change in stimulus to accommodation. For example, in Figure 1*B*, the change in stimulus to accommodation produced by +2 D. spheres before the eyes causes an ocular-motor imbalance corresponding to a measured exo-disparity of about −8.7 minutes of arc (Point P_1). Going to Figure 1*A*, we find that the same exo-disparity is also produced by putting 10Δ base-out before the eyes (5Δ prisms before each eye) (Point P_2). In Figure 1*C* we plot the point on the abscissa +2 D. change in stimulus to accommodation, and on the ordinate, +10Δ base-out (Point P_3).

This procedure is repeated for the whole series of spherical lenses used, and a series of points is obtained, as shown in Figure 1*C*, that falls fairly well on a straight line. The line that best fits the derived data points is drawn visually.* The slope of this line is the measure of the ratio of the equivalent forced convergence corresponding to a given change in the stimulus to accommodation.

* Frequently it has been found that if the complete prism-disparity data are obtained first, and then the lens-disparity data are obtained, the disparity at the origins will be slightly different. This difference causes a vertical displacement of the derived data line. Comparison with data taken using prisms and lenses alternately shows that the slopes of the derived data lines by the two techniques are relatively unaffected. This difference in imbalance points out the importance of residual effects of previous prism vergences and stimuli to accommodation-to-phoria data.[4]

This slope is the desired ratio, that is, the ratio of the accommodative convergence to the accommodation—abbreviated (A−C)/A. In Figure 1*C*, (A−C)/A is 5.2Δ/D. (prism diopters per diopter). The present study consisted in finding the (A−C)/A, the slope of these derived data lines, for subjects whose eyes were under the influence of certain drugs.

Ten persons between the ages of 20 and 31 years, whose vision was fully corrected for refractive errors, served as subjects for this study. After the "normal" curves had been established from at least two sets of measurements, data were taken with (1) dilated pupils, (2) pupils made smaller with minimal or absent ciliary (accommodative) spasm, and (3) pupils made smaller with ciliary spasm.

Mydriasis was produced by the use of a sympathomimetic amine, 10% solution of phenylephrine hydrochloride. This strength was selected rather than a weaker one because of the maximal mydriasis obtained, albeit there might sometimes be a slight cycloplegic effect. Miosis was obtained with a 0.5% solution of pilocarpine hydrochloride, a parasympathomimetic agent (cholinergic, muscarinic). This strength produced excellent miosis with little if any clinical evidence of a ciliary spasm. To obtain miosis with concomitant spasm of the ciliary muscle, 2% solution of pilocarpine nitrate was used. The accommodative change was evident by a decrease in visual acuity, the approach of the far point, and the ability to accept higher than normal minus spheres. In two subjects 0.25% solution of physostigmine sulfate was used. Several days usually elapsed between tests. Just preceding each test, the size of the pupils was measured to an estimated 0.5 mm. with a millimeter rule. As became evident, greater accuracy was not essential. Attempts to determine the near point of accommodation by a "push-up" method were unsatisfactory because of the large depth of focus when the eyes were under the influence of pilocarpine. Retinoscopic examination proved more satisfactory, but this examination could be made completely for only several of the subjects.

Results

1. *Phenylephrine.*—The purpose of studying the effect of phenylephrine was to learn to what extent the enlarged pupil size alone was a factor in the marked increase in the (A−C)/A ratio found with homatropine. With the eyes under the influence of phenylephrine hydrochloride (2 drops of 10% solution) as used in these experiments, one would expect the accommodative processes to be unaffected by the drug. Consequently, one would not expect any change in the accommodation-convergence association [as expressed by (A−C)/A ratio] until the change in the stimulus to accommodation approached the limit of the accommodative range (both plus and minus spheres). If the stimulus to accommodation is somehow related to blur of the retinal image, with the large pupil one would expect a larger blur to be associated with smaller degrees of change in lens power and, therefore, an increase in the (A−C)/A ratio at the ends of the range. Actually, a study of the derived data shows that if there is any departure from linearity of these data it is in the direction of a decrease rather than an increase. However, for that range of stimuli to accommodation outside the accommodative range, as the blur of the retinal image becomes greater than that caused by unfocused images of about 1.5 D. of refractive error,[5] some decrease might be expected.

The effect of phenylephrine is shown in the Table. Tabulated for each subject are the pupillary diameter, the (A−C)/A ratio, and the equivalent phoria, which is that prism vergence at which there is no ocular-motor imbalance (disparity is zero). Inspection of the Table shows that, in spite of some individual variations, a nearly two-fold increase in diameter of the pupil has not significantly altered the (A−C)/A ratio or affected the equivalent phoria within the errors of measurement. An inspection of the

Summary of Pertinent Results of Study of the Effect of Phenylephrine and Pilocarpine on the Accommodation-Convergence Association

Subject	Normal			10% Phenylephrine			2% Pilocarpine			
	Pupil, Mm.	(A—C)/A, Δ/D.	Equivalent Phoria, Δ *	Pupil, Mm.	(A—C)/A, Δ/D.	Equivalent Phoria, Δ *	Pupil, Mm.	(A—C)/A, Δ/D.	Equivalent Phoria, Δ *	Displacement, Δ *
1	3	2.6	3.5 s	8	2.8	5.5 s	1.5	2.5	1.5 s	2.0 x
2	3	3.7	6.5 x	6	3.7	7.5 x	1.5	3.7	11.5 x	5.0 x
3	4	1.9	7.0 x	7	2.8	5.5 x	1.5	1.8	14.0 x	7.0 x
4	--	5.2	1.0 x	7	4.6	0.5 x	1.5	4.9	7.0 x	6.0 x
5	7	3.6	7.0 x	7	4.4	6.5 x	2	2.9	14.0 x	7.0 x
6	6	5.3	0.0	8	4.0	0.0	1.5	4.7	4.0 x	4.0 x
7	5.5	3.0	0.0	7	0.9	0.0	1.5	3.5	5.0 x	5.0 x
8	4.5	6.2	9.5 s	9	6.2	7.5 s	1.5	3.5	3.5 s	6.0 x
9	4	2.9	7.0 x	8	3.7	8.5 x	1.5	3.2†	11.0 x	4.0 x
10	3	5.3	6.0 x	7	4.8	5.5 x	1.5	5.1	13.5 x	7.5 x
Average	4.4	4.0	2.15 x	7.4	3.8	2.10 x	1.5	3.3	7.5 x	5.4 x
Standard deviation		1.3			1.3			1.0		1.6

* s, esophoria, prism diopters; x, exophoria, prism diopters.
† Average of two sets.

original data shows also that "fixation-disparity prism-curves" are essentially the same with and without the phenylephrine.

2. *Pilocarpine.*—The results obtained with subjects in whose eyes pilocarpine was instilled are of particular interest, because this drug causes a marked miosis and usually some contraction of the ciliary muscle, with a concomitant effective change in the accommodative state of the eyes. This drug is believed to act directly on the neural motor end-plates in the ciliary muscle, causing an increase in tonicity—a contraction and an increase in the accommodative state of the eye.

Figure 2 shows the curves from the data of an esophoric subject, obtained before and after the instillation of 2 drops of 2%

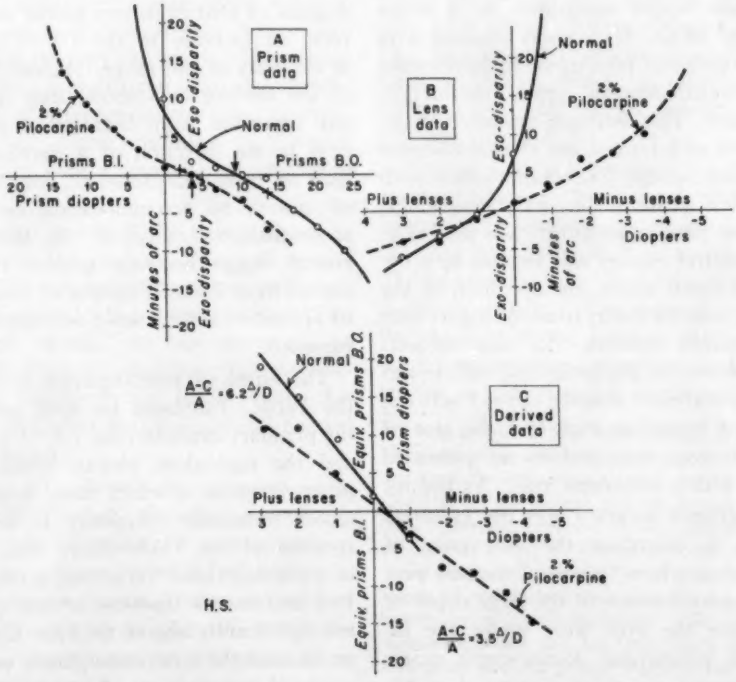

Fig. 2.—Fixation-disparity curves showing the effect of pilocarpine for an esophoric subject.

pilocarpine hydrochloride in the conjunctival sacs of both eyes. For this particular subject one notes the following when the eyes are under the influence of pilocarpine: 1. There is a shift of the prism-disparity curve in the direction of an exophoria. Here the esophoria has actually been decreased from 9.5Δ to 3.5Δ (Fig. 2*A*). 2. There is a decrease in the accommodative convergence-accommodation ratio, (A−C)/A (Fig. 2*C*). This subject showed the greatest change with the pilocarpine of any of the 10 subjects. 3. The accommodation-convergence relationship is linear within the range for which data could be obtained. 4. The same geometric curve describes the points obtained for the prism-disparity data with and without the drug.

Figure 3 illustrates the data of a second subject with marked exophoria. With the eyes under the influence of pilocarpine, again one notes the following: 1. There is an increase in the exophoria, a shift of the prism-disparity curve of 5Δ to the left (Fig. 3*A*). 2. The (A−C)/A ratio, the slope of the derived line, is slightly, but probably not significantly, increased, from 3.0Δ to 3.5Δ per diopter change in stimulus to accommodation (Fig. 3*C*). 3. The derived line departs slightly from linearity for the highest minus power lenses used. This departure from linearity was not typical of the other nine subjects. 4. The same geometric curve describes the points obtained for the prism-disparity data with and without the drug.

The summary of the (A−C)/A ratios for the 10 subjects, the slope of the accommodation-convergence association lines, is shown in the Table. The pupillary diameters, the (A−C)/A ratios, and the equivalent phorias are given. There are individual differences, which probably represent different reactions to the drug, as well as normal physiologic variations. However, with a comparison of the mean values and standard deviations for the entire group of subjects, it is questionable whether there is a trend toward either a higher or a lower (A−C)/A ratio resulting from the drug. The mean values of the ratios obtained with drugs

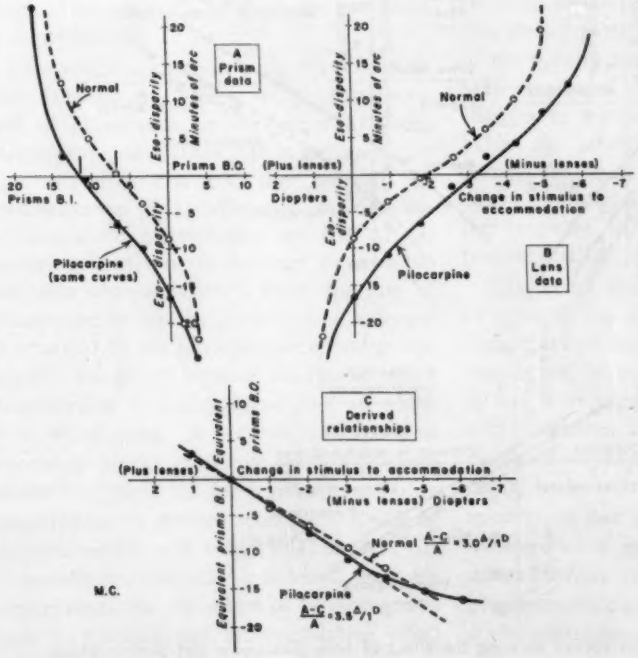

Fig. 3.—Fixation-disparity curves showing the effect of pilocarpine for an exophoric subject.

compared with the normal ratio values certainly do not indicate a significant difference.

Of special interest is the last column, which gives the difference between the equivalent phorias obtained with and without pilocarpine. These differences give the amount of exophoria induced indirectly on the accommodation by the effect of the drug under the conditions of this study. The displacement of the prism-disparity curve, as measured by the displacement of the equivalent phoria in the direction of an exophoria, is approximately of the same order for the 10 subjects tested (average, 5.4△). It is probable that this displacement of ocular-motor imbalance is related to the degree of change in accommodation caused by the drug. This would vary with the concentration of the drug, the number of times instilled, the method of instillation, and other factors. This phenomenon of a displacement of the phoria is undoubtedly the same as that which occurs when isofluorophate (DFP) is used in cases of accommodative-convergent squint, and where an effective exophoric displacement of ocular-motor imbalance occurs.[6,7]

How are we to explain the displacement of the motor imbalance (prism-disparity curve, and so forth) in the direction of exophoria? One could argue that, if the drug were to cause a maximal accommodation, that is, cause a complete regression of the far point to the near point of accommodation, one could explain the phenomenon on the basis of the blur of the retinal image produced by objects beyond the near point. This type of blur would then stimulate a relaxation of accommodation, and this stimulus would result in a divergence impulse through the accommodation-convergence synkinesis.

Since the amount of effective accommodation caused by the drug in the present experiments was usually not large, however, the probable explanation of the phenomenon

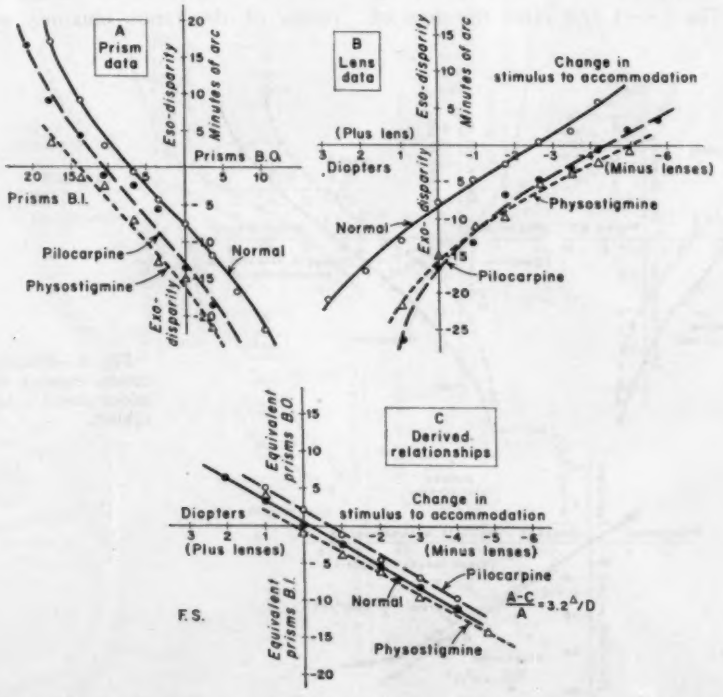

Fig. 4.—Fixation-disparity curves showing the effect of both pilocarpine and physostigmine.

lies in the fact that the effective accommodation caused by the pilocarpine, since it is noninnervational, is not associated with an accommodative convergence. Hence, the accommodative convergence changes produced by further innervational stimuli would start at the accommodation level produced by the drug, that is, at a relative divergence (exophoric) position. Siebeck [8] has pointed out that pilocarpine acts on the accommodation as an independent stimulus and that its effect is purely additive to the accommodation resulting from a nerve impulse.

3. *Physostigmine.*—For two subjects physostigmine was used. The results were similar to those obtained when pilocarpine was used. Figure 4 illustrates the results from one subject. The (A−C)/A ratio is relatively unaffected by either the pilocarpine or the physostigmine. The data for the second subject show a small lowering of the (A−C)/A ratio. The shift of the equivalent phoria in the exophoric direction is greater than that for the pilocarpine. No conclusions can be drawn from this fact, however, because the amount of absorption of the drug or its relative activity in the two cases is unpredictable.

One would not expect a significant difference between the effects of physostigmine and of pilocarpine on the accommodation-convergence association. It is believed that physostigmine restricts the amount of cholinesterase that ordinarily rapidly decomposes the acetylcholine set free at the parasympathetic nerve endings by a nerve stimulus or innervation.[9] Thus, the rate of decomposition of the acetylcholine released is retarded by the physostigmine, and a new equilibrium occurs between the rate at which acetylcholine is released and that at which it is decomposed. A nervous stimulation is necessary for the release of the acetylcholine in the first place, but for a given innervation once released a greater accumulation will be present, which will cause an excessive accommodation. Siebeck [8] concluded from his experiments that the effect of physostigmine was to multiply the accommodative effect initiated by the nerve impulse from a stimulus to accommodation. On the other hand, Fincham,[10] in his study of convergent accommodation, showed that physostigmine essentially added a certain amount of accommodation to that initiated by a change in convergence alone. In our experiments the accommodative convergence, initiated by a change in the stimulus to accommodation, according to either of the foregoing findings somehow would be related to the stimulus arising from a blurring of the retinal image. Thus, this stimulus to an accommodative change would be independent of the effect of the physostigmine itself. Hence the same accommodative convergence [the normal (A−C)/A ratio] would be expected.

The fact that the accommodation-convergence response was of the same order for normal eyes as for those under the influence of pilocarpine, where the pupil size becomes so small, deserves comment. With the pupil as small as 1.5 mm. the depth of focus of the eye will be large, and hence on the basis of out-of-focus blur of the image there would be little stimulus for accurate accommodation. However, as our data show, the regular convergence response of the eyes to lenses indicates that the eyes have responded regularly and accurately to changes in stimulus to accommodation.[11,12] When the stimulus to accommodation lies outside the range of the available accommodative amplitudes (restricted by the drug), the response still continues regularly and proportionally.

This result brings us to the old problem of what is the stimulus to accommodation. Simple out-of-focus blur of the retinal image would not be a satisfactory answer here. It has been suggested that the stimulus to accommodation arises from chromatic aberration effects in out-of-focus images,[6] which would be less influenced by pupil size. The assumption has been made that the contrast differentiation in the various parts of the image blur, by virtue of the Stiles-Crawford phenomenon, especially with eye movements, could contribute as a stimulus to accommo-

dation. However, it would not seem reasonable that the Stiles-Crawford phenomenon could account for the results here, when the pupil is so small. The vergence of the rays at the retina would be too small. It is also questionable whether the "psychic awareness of distance" would be sufficiently changed by the power lenses used at a constant observation distance to be a factor. It is possible that searching-like random changes in the accommodation or physiologic fluctuations in the accommodation could lead to sharp imagery.

Summary

It has been previously shown that the accommodative convergence increases markedly when homatropine is instilled into the eyes. The problems studied here are the influence of the large pupil in that situation and, more important, the effect of such drugs as pilocarpine and physostigmine on the accommodative convergence, where miosis and spasm of accommodation occur. The results from data obtained by the fixation-disparity technique show that phenylephrine (Neo-Synephrine), which dilates the pupils but has little effect on the accommodation, caused no change in the accommodative convergence within the precision of measurement. The linear relationship between the accommodative convergence and change in stimulus to accommodation was generally maintained throughout the range of response. With pilocarpine the linear relationship was held also, and, although there were individual differences, the average of the accommodative convergence in a group of 10 subjects showed no significant change from the average found without the drug. With two subjects the effect of physostigmine was essentially the same as that of pilocarpine. These results are discussed with reference to the mode of action of the drugs and to the relationship of the small pupil to the stimulus to accommodation.

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Studies on Simulated Vitreous Hemorrhages

II. The Effects of Lytic Enzymes, Surface-Active Agents, and Urea

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There have been a number of reports on the modification of the vitreous body by lytic enzymes but few, if any, on the effect of surface-active agents (surfactants) and urea.

In the early work with hyaluronidase, von Sallmann [1] and Pirie [2] found that this enzyme produced considerable inflammation in the vitreous. Subsequent purification of the hyaluronidase has reduced the amount of inflammation produced. Planten and Hoppenbrouwers,[3] using a small amount of hyaluronidase, found little inflammatory reaction after intraocular injection.

A preparation of streptokinase and streptodornase (Varidase) has been studied, with somewhat conflicting results. Jukovsky [4] claimed that streptokinase-streptodornase produced lysis of blood clots in the anterior chamber of rabbit eyes, while Friedman [5] found that it produced very little lysis and caused a damaging inflammation. O'Rourke [6] showed that blood clots were slowly lysed by streptokinase-activated plasminogen and that at concentrations greater than 50,000 units per cubic centimeter corneal opacification was produced with a 0.2 ml. intracameral injection in the rabbit. He suggested that the inflammation might be due to hyaluronidase present in the enzyme preparation.

A collagenase preparation from Clostridium perfringens (C. welchii) was found by Pirie, Schmidt, and Waters [7] to liquefy the vitreous of ox eyes. The insoluble residual protein of the vitreous was hydrolyzed to a variable extent by the enzyme.

Many surface-active agents, or surfactants, have the property of modifying protein structure. Saponin and phenylhydrazine (used clinically to lyse red cells) and the synthetic surfactants are members of this group of chemicals. The synthetic surfactants are of three chemical types: anionic, cationic, and nonionic.

Urea solutions also modify and solubilize proteins, and so a study of the effect of this substance on the vitreous was of interest.

We have studied the effect of lytic enzymes (including those mentioned above), surfactants, and urea on the vitreous bodies of rabbits. The effects were observed by ophthalmoscopic and histopathologic examination of the eye. The influence of these agents on the rate of disappearance of radiochromium-tagged simulated hemorrhage in the vitreous was determined by radioactivity measurements.

Methods and Materials

A simulated hemorrhage was produced in the vitreous of rabbits by injection of radiochromium-tagged red blood cells as described in our first article.[8] During the period of steady rate of disappearance of radioactivity from the eye, 0.05 ml. or less of enzyme, surfactant, urea, or a control solution of isotonic saline solution was injected into the posterior vitreous.

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Radioactivity measurements were recorded and the resulting data were handled as reported previously.[8]

Results and Comment

Enzymes.—(*a*) Hyaluronidase*: When used at a level of about 3000 T. R. U. (turbidity-reducing units), hyaluronidase produced transient mild iritis. This was followed by formation of strands or sheaths running from the lens to the optic nerve. The amount of liquefaction of the vitreous was somewhat variable. The rate of disappearance of radioactivity was not changed by the injection of this enzyme.

(*b*) Streptokinase-Streptodornase: A considerable inflammatory reaction of the iris and retina was produced by streptokinase-streptodornase (13,000 units of streptokinase and 2160 units of streptodornase).† The rate of decrease of radioactivity in the eye was unaffected.

(*c*) Collagenase: Preliminary studies on collagenase from C. perfringens‡ showed it to produce a marked inflammation at the 50μg. level. Considerable work was done in an attempt to purify the preparation, with the hope of separating the lytic effect from the inflammatory reaction. Continuous-flow paper electrophoresis of both collagenase and a collagenase-antiserum mixture produced a purified enzyme, although the resultant product still caused marked damage to the retina and lens. Fifty-microgram amounts of the collagenase preparation from C. histolyticum,§ although free of γ-toxin (hyaluronidase), also caused inflammation. These preparations were without effect on the rate of disappearance of radioactivity.

(*d*) Trypsin: In amounts of 200μg. or less, trypsin (Tryptar, Armour), caused only a mild and transient chorioretinitis, while the use of larger amounts was associated with retinal degeneration and cataract formation. The disappearance rate of radioactivity is unaffected by this enzyme.

Surface-Active Agents.—(*a*) Saponin: It was calculated from the data of Bunting[9] that the amount of saponin necessary to lyse the red blood cells of the simulated hemorrhage in the rabbit eye should be 3.8μg. At this level, saponin (Merck) had no effect on the vitreous or on the rate of removal of hemorrhage. Considerably higher levels (75μg. and 125μg.) caused chorioretinitis, retinal necrosis, and an interesting and characteristic vacuolation of the epithelium of the ciliary body.

Lysis of the blood cells apparently is not a limiting reaction in removal of hemorrhage from the vitreous, since saponin showed no effect on the rate of disappearance of radioactivity.

(*b*) Phenylhydrazine: This material, in the small amount (23μg.) which was calculated to be sufficient to lyse red cells,[10] was without effect on the eye. Twenty times this amount produced an inflammatory response, chorioretinitis, and retinal degeneration. It was without effect on the rate of disappearance of the simulated hemorrhage.

(*c*) Synthetic Surfactants: An alkyl aryl sulfonate (Oronite NIW), an example of a nonionic surfactant, produced only minor pathological effects when a solution containing 0.6μl. (microliter) was injected. The cationic material (alkenyldimethylethylammonium bromide) caused chorioretinitis, inflammation, and degeneration of the iris and ciliary body when a solution containing 0.2μl. of a 10% solution was injected. The anionic surfactant (sodium lauryl sulfate) was also highly inflammatory. These compounds were without effect on the rate at which the radioactive blood left the eye.

Urea.—The residual proteins of the vitreous are, in large measure, a type of collagen and, as such, are expected to exhibit

* A concentrated preparation, 6300 T. R. U. per milligram, was provided by Wyeth Laboratories, Inc., Philadelphia.

† Lederle Laboratories Division, American Cyanamid Company, Pearl River, N. Y.

‡ Provided by Wellcomb Research Laboratory, Kent, England. Since this preparation contains γ-toxin (hyaluronidase), a specific antiserum was also provided.

§ Lederle Laboratories.

a definite shrinkage temperature (the temperature at which a collagen fiber, when slowly heated in a physiological solution, abruptly contracts). When collagen is bathed in solutions of urea the shrinkage temperature is lowered.[11] This process of shrinkage is, in effect, a denaturation process, and when denatured, collagen is subject to hydrolysis by trypsin. Treatment of whole beef vitreous with an equal volume of 10 M urea at 37 C for 26 hours causes shrinkage of the entire vitreous. Simultaneous treatment with trypsin, 1 mg. per milliliter, produces a clear solution with a few floating particles. In vivo, only approximately 2 M final concentration of urea could be obtained, because of the dilution by the vitreous humor of the 0.2 ml. of 10 M urea solution injected. The clear-cut liquefaction observed in vitro was not attained.

This treatment did, however, cause an increase in the rate of disappearance of radioactivity from the vitreous; the half-times of the rapid phase of the curve were reduced in several cases to less than three days, which is the normal biological half-life of these hemorrhages (see the preceding article [8]). This is shown in the Table. This effect is more clearly shown in the case of smaller simulated hemorrhages and appear to be due to the urea, because it occurs whether or not trypsin is used in conjunction with the urea. There is considerable inflammatory response, however, resulting in chorioretinitis with degeneration of the retina.

Summary

The effects of enzymes, surface-active agents, and urea on radioactively tagged vitreous hemorrhages in rabbits were studied.

The enzymes and the surface-active agents caused ocular damage, the amount and nature of the damage depending upon the specific material and its concentration. These materials were without effect on the rate at which the radioactivity left the eye.

Urea was the only agent which accelerated the rate at which radioactivity left the eye. This effect was more pronounced with smaller hemorrhages. However, the pathologic effects of urea make the use of this substance impractical.

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Summary of Results

Rabbit	Blood, Volume of	10 M Urea		Trypsin		Half-Time Curve 2 *	Day of "Break" *	Half-Time Curve 3 *
		µl. Injected	Day of Injection	µg. Injected	Day of Injection			
504	0.10	25	8			3	11	40
511	0.10	50	8			3	11	44
508	0.10	100	8			2	11	50
506	0.10	25	8	200	8	3	11	50
503	0.10	50	8	200	8	3	11.5	50
509	0.10	100	8	200	8	2	11	17
603	0.10	100	3	200	10	4	7	24
606	0.10	100	3	200	10	3	7	32
607	0.10	100	3	200	10	1	6.5	10
605	0.05	100	3			1	6	7.5
611	0.05	100	3			1.5	7	17
608	0.05	100	3	206	10	1	6	11
609	0.05	100	3	200	10	1.5	6	9
Controls								
610	0.05					3	10	23
612	0.05					3.5	15	30

* See previous paper.[8]

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Agenesis of the Medial Rectus Muscle

Correction of a Case by Transplantation of Slips from the Vertical Recti

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The purpose of this report is to describe a case of agenesis of the medial rectus muscle which was corrected by transplantation of muscle slips from the vertical recti. Relatively few cases of agenesis of the extraocular muscles have been reported. Three cases of absence of the lateral rectus, three cases of absence of the medial rectus, two cases of absence of the superior rectus, four cases of absence of the inferior rectus, two cases of absence of both the inferior and superior recti, one case of absence of both obliques, and one case of absence of both superior obliques are cited by Duke-Elder (1949).[1]

Report of Case

A female girl, was first examined at the age of 2 months. At that time, the corneal reflex test elicited a right exotropia of approximately 50△. She would not follow a light. Her family and birth history revealed that she was the parents' fourth child and weighed 8 lb. 13 oz. at birth; she was born after a labor of 14 hours. There was a family history of myopia, and one sibling had died soon after birth from obscure causes.

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From the Department of Ophthalmology, Baylor University College of Medicine, Houston, Texas.

During the neonatal period she had difficulty with excessive mucus in the trachea, which caused several episodes of anoxia, and she remained in the hospital nursery two days after her mother was discharged. These anoxic episodes continued at infrequent intervals during the first three months of life. An electroencephalogram showed a normal tracing.

The patient was reexamined at the age of 4 months, and the deviation was noted to be unchanged; that is, there was a right exotropia of about 50△. At this time she followed a light in the six diagnostic positions of gaze. There was a suggestion of weakness of the right superior rectus, but the striking finding was her inability to adduct the right eye past the midline (Fig. 1).

The left eye was occluded constantly for two weeks, but at the end of this period the right eye still could not be adducted past the midline. Ductions of the left eye appeared normal.

At the age of 8 months, it was believed that surgical exploration of the horizontal rotators of the right eye was indicated. Before surgery was begun and while the child was under general anesthesia and mydriasis, the ocular fundi were examined. The left fundus appeared normal for her age. The right eye showed an estimated 5 D. of myopia; the nerve head was pale, and no foveal reflex could be seen. Surgery was then begun, and the right lateral rectus was picked up and cleaned free of dense check

Fig. 1.—Preoperative findings. Note that the right eye moves to the midline in levoversion but shows no adduction beyond this point.

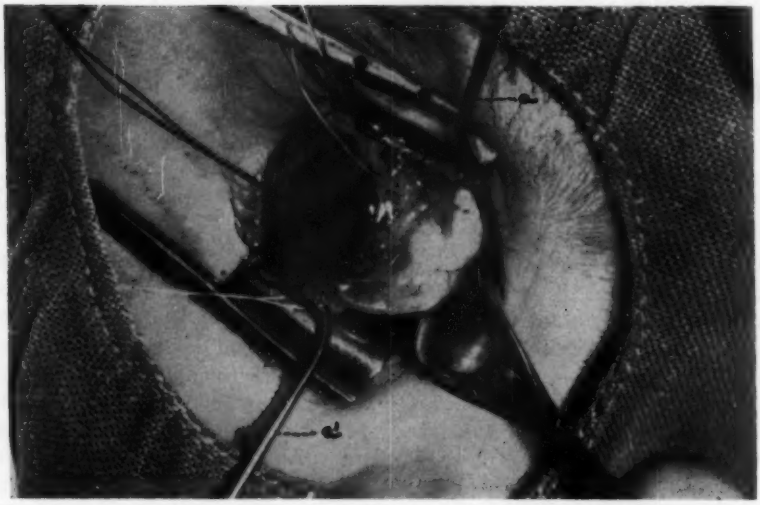
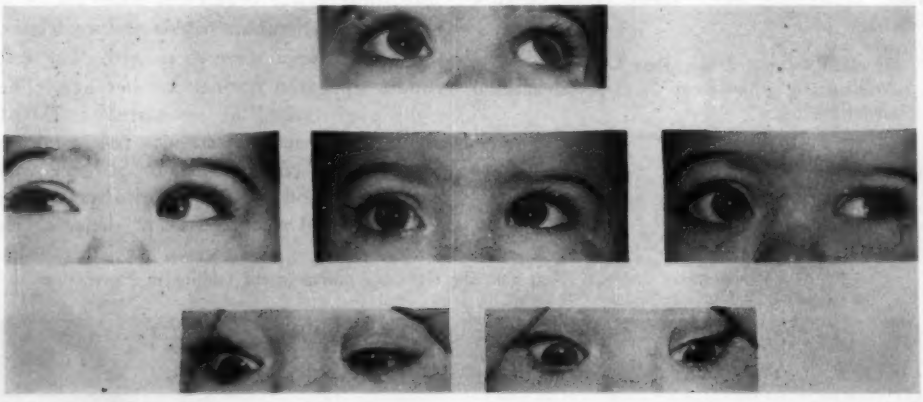


Fig. 2.—Findings at operation. The eyeball is rotated temporally, and the superior and inferior recti are isolated on muscle hooks (a,a'). Structures on the nasal side have been retracted to show bare sclera at the site of the normal medial rectus insertion.

ligamentous attachments to the lateral wall of the orbit; it was then severed from its attachment to the eyeball and retroplaced 7 mm. from its original insertion. The conjunctiva was incised over the position of the right medial rectus. Attempts to identify the muscle revealed that no right medial rectus was present (Fig. 2). In view of this finding, the conjunctival incision was extended over the insertions of the vertical recti, which were isolated on muscle hooks. The temporal halves of both vertical recti were severed (Hummelsheim operation) and brought under the medial halves and sutured to the sclera 5.5 mm. from the limbus with 00000 white nylon at the site where the insertion of the medial rectus should have been. The conjunctival incision was closed with a running 00000 plain absorbable surgical (gut) suture. During the postoperative period there was moderate reaction, and after one week the right eye could be adducted past the midline.

Three months after surgery the patient could fuse in the primary position and could adduct and abduct the right eye about 10

Fig. 3.—Postoperative findings. The right eye can be adducted 10 to 15 degrees.



to 15 degrees (Fig. 3). No vertical imbalance was noted.

Comment

This case is interesting not only from the standpoint of congenital absence of an ocular muscle but also from certain physiologic aspects.

In the primary position, the patient demonstrated a right exotropia of 50△ (25 degrees), indicating that the right lateral rectus was acting unopposed. On levoversion the right eye demonstrated movement to the left (adduction), reaching the midline. The absence of the medial rectus brings up the interesting question as to which muscles participated in this movement.

It is the general consensus of physiologists that in horizontal movements all of the muscles of the eye except one contract. Adler [2] has stated:

> In looking laterally from the primary position the lateral rectus receives a stimulus to contract while the medial rectus is simultaneously inhibited, losing some of its tone, according to the law of reciprocal innervation. At the same time, all of the other muscles also receive a stimulus to contract. The superior and inferior recti, by contracting, counterbalance each other's vertical action, so that the eye does not swerve up or down from its horizontal path. These two muscles also counterbalance each other's torsional action, so that the vertical meridian is held vertical. With the eye in the primary position, both muscles combine to adduct the eye and hence, oppose to a moderate degree the outward movement. By their steady pull, they prevent the outward movement from taking place too suddenly or jerkily. The two obliques contract and also counteract each other in torsional and vertical action. Thus, they also act to steady the eye in its course, but at the same time, these muscles abduct the eye and so reinforce the action of the lateral rectus. At the beginning of the movement from the primary position, their abducting action is about neutralized by the adducting action of the superior and inferior recti. At the beginning of the movement, the lateral rectus is the prime muscle exerting abduction, and in this position, it is working at a considerable mechanical advantage. As the eye turns out, however, it loses this advantage, since its arc of contact is being used up and also, since it is increasingly opposed by the lengthening and stretching medial rectus. As the power of the lateral rectus diminishes, however, the abducting action of the obliques come more and more into play, since their action as abductors increases as the eye is turned outward. Further, the counteracting action of the superior and inferior recti falls off altogether when the eye has been turned out 23° from the primary position.

What has been stated by Adler regarding the muscles involved in the movement of abduction may be applied to the movement of adduction. In other words, in adduction of the eyeball the prime muscle exerting adduction would be the medial rectus, with the vertical recti coming into play as adductors as the eye turns inward.

In our patient, the right eye was at rest in a position 25 degrees temporal to the primary position, which theoretically is beyond the point where the superior and inferior recti can act secondarily as adductors of the eyeball. Yet the patient still demonstrated some adduction of the eyeball. The only explanation for this phenomenon which occurs to us is that even when the eyeball is placed in the muscle plane (plane of action) of either the vertical recti or the obliques some secondary action of these muscles can be accomplished. Theoretically, therefore, if both the medial and lateral recti were severed, there would be some horizontal rotation of the eyeball.

The second interesting physiologic aspect of this case concerns the adduction which resulted after transposition of slips from the vertical recti. While many authors have reported good results with the Hummelsheim operation or one of its modifications, others have questioned whether it is actually possible to develop powers of abduction or adduction when halves of the vertical recti have been transplanted. Since all of the reports, thus far, have dealt with paralysis of the lateral rectus, opponents of this procedure have questioned whether abduction obtained was from the transplanted slips of the vertical recti or from the resected paralyzed lateral rectus. Their objections have been summarized by Scobee [3] (1952), who stated:

> In recent years, however, it seems to be the consensus of those who know best that [the

Hummelsheim operation] should always be performed in two stages for the reason that the second stage, which was never entirely satisfactory, may often be unnecessary. In other words, the first operation on a patient with a complete paralysis of the lateral rectus should be confined to a maximum recession of the antagonistic medial rectus and a maximum resection of the paretic lateral rectus. The direct results are often amazing in that the patient may not only get the paretic eye into the primary position, but may also manifest some slight degree of abduction.

Payne[4] (1943) reported on two cases of lateral rectus paralysis. One was treated in the manner described by Scobee, and on the other the Hummelsheim procedure was performed. Good abduction was obtained in both cases.

The proponents of the Hummelsheim procedure point to the work of Marina,[5] in 1915; Olmstead, Margutti, and Yanagisawa,[6] in 1936, and Leinfelder and Black,[7] in 1941 and 1942, for a scientific explanation of the results of this operation.

In 1915, Marina reported a return to normal function following the transposition of the medial and lateral recti in experimental animals. This work received little attention, but, in 1936, it was confirmed by the research of Olmstead, Margutti, and Yanagisawa. The results obtained by these investigators suggested that the anatomic relationship of the extraocular motor apparatus is not so fixed as had previously been believed, since following transposition the muscle apparently executed rotation that differed from the original function. Moreover, after transposition of the muscle, it not only takes over a new function but also coordinates with its new associate in the eye on which no surgery has been performed. Leinfelder and Black found that as long as two of the six oculorotary muscles were left intact, any or all of the remaining four might be transposed indiscriminately and the recovery of coordination would still occur. If a sufficient interval between the transposition was allowed five of the six oculorotary muscles might be transposed with recovery of coordination. Berens and Girard[8] (1950) reviewed the results of transplantation of portions of the superior and inferior recti for lateral rectus paralysis in 62 cases reported by other surgeons and added 7 cases of their own.

The result obtained in the subject of the present report apparently lends weight to the argument in favor of the Hummelsheim procedure. In this patient no medial rectus existed, and, therefore, the adduction obtained could not have occurred from resection of a previously paralyzed muscle.

Still another interesting physiologic aspect is the degree of reaction which occurs postoperatively in patients who have had transposition of muscles. Leinfelder and Black (1941), in their experiments with the Rhesus monkey (Macaca mulatta), reported one eye lost owing to infection, several cases of mild iridocyclitis, and one case of a heminecrosis of the iris and persistent localized dilatation of the pupil. One of us (L. J. G.) has performed muscle transplantation operations on two adults, employing the technique as described by Berens and Girard, in which the operations were followed by severe keratitis, iridocyclitis, necrosis of the iris, and secondary cataract. Evidently, surgery on four rectus muscles interfered with the anterior ciliary circulation sufficiently to produce this reaction. The fact that these complications occurred in adults and had not been observed in 11 children operated on previously suggests that the anterior ciliary circulation is more important to the nutrition of the anterior segment in the adult than in the child. The original Hummelsheim procedure, leaving one-half of each vertical rectus intact, was employed in the case presented.

Summary

A case of agenesis of the medial rectus muscle with inability to adduct the eye past the midline is presented. This deficiency was corrected by transplantation of slips from the vertical recti, and, as a result, the patient could fuse in the primary position and adduct the affected eye.

The case is discussed from three physiologic aspects which are of interest: (1) ability to perform some adduction in the absence of the medial rotator, (2) improved adduction after transplantation of slips from the vertical recti, and (3) the possibility of iris necrosis and iridocyclitis after surgery involving all four rectus muscles.

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Human Amnion-Cell Tissue Culture

A Study of Herpes Simplex and Adenovirus

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Introduction

In the study of viruses infecting the eye, a method of virus isolation has been sought which is simple, inexpensive, and yet permits rapid and reliable identification of the virus. Amnion tissue seems to afford such a means of virus identification.[1,2] 1. Amnion is an inexpensive source of cells—readily prepared and maintained with commercially available media. 2. A single amnion can yield many hundred roller tubes, which may be stored so that a single amnion can furnish a supply of roller tubes for two to three months.[3-5] 3. A wide spectrum of viruses can be grown in amnion: the herpes zoster-varicella group, poliomyelitis virus, most ECHO viruses, many of the coxsackie group, croup-associated virus, measles, and others.[1,3-5] 4. Many viruses, especially herpes simplex and the adenoviruses, produce characteristic cytopathogenic changes that are readily detected. These changes are more easily seen and develop earlier than would be expected in many other tissues (for example, monkey kidney and HeLa cells).[6-10]

It is the purpose of this communication to report the cytopathogenic changes with herpes simplex and adenovirus and some additional properties of the tissue.

Methods

Amnion Cells.—Both roller tubes and "flying coverslips" were supplied by the Department of Infectious Diseases of the Children's Medical Center, Boston. They were prepared either by modifications of the method of Rappaport[6,11] or by the method of Weinstein.[12] *

Virus Specimens.—The species of herpes simplex virus studied were isolated from corneal scrapings of patients at the Massachusetts Eye and Ear Infirmary. The identity of all virus was confirmed by neutralization tests against serum with known herpes simplex antibodies. Studies were also repeated with "stock" herpes simplex virus.

Adenovirus studied was stock virus of known type, previously determined by neutralization test. Types 1 through 12 were used.

Roller tubes and coverslips of human amnion-cell monolayers in CAF medium † were inoculated with virus and kept in a roller wheel at 37 C. CAF medium was changed before inoculation and thereafter upon becoming acid.

Observations were made on unstained roller tubes and on unstained coverslips with ordinary light and phase-contrast microscopy. In addition, stained coverslips and stained collodion-imbedded roller-tube sheets were used. All herpes-simplex-infected cells and many adenovirus-infected tissues were fixed in methanol 94%, formalin 5%, and acetic acid 1%, though some adenovirus-infected preparations were fixed in Bouin's fixative. Tissues were fixed for ½ to 24

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The Howe Laboratory of Ophthalmology of the Massachusetts Eye and Ear Infirmary and the Department of Medicine of the Massachusetts General Hospital, Boston.

* Ammiotic tissue culture tubes are not prepared commercially by Microbiological Association, Inc., 4846 Bethesda Ave., Washington 14, D. C., and are grown by them in Eagle's Basic Medium with 10% Human Serum.

† 45% Cow amniotic fluid, 45% Hank's Balanced Salt Solution, 5% beef embryo extract, and 5% inactivated horse serum.

hours and stained with Harris' hematoxylin and eosin. Progression of changes was observed in each case by using the same inoculum of a given virus in each of several tubes. A control specimen of the same batch of amnion was paired with each inoculated specimen observed. Both stained and unstained preparations were studied after degeneration caused by aging and nonspecific toxicity.

Results

Herpes Simplex.—General Cytopathogenic Changes: Clusters of round refractile cells were consistently found after amnion infection with herpes simplex. Characteristic changes were seen within 12 to 24 hours after inoculation, though observation for 48 hours was sometimes necessary, especially when the amnion cells were granular at the start. Degeneration began with the appearance of small discrete areas of these round, granular, refractile cells. This initial phase of isolated clusters of succulent round cells, appearing in an otherwise normal sheet, was very definite. These clusters enlarged and became more numerous with time, disrupting the continuity of the sheet. The final stage of infection was characterized by complete dissolution of the cell sheet and cell death, with only clumps of the rounded refractile cells visible (this terminal stage being nonspecific and seen after toxic degeneration or cell death from other causes) (Figs. 1 to 3).

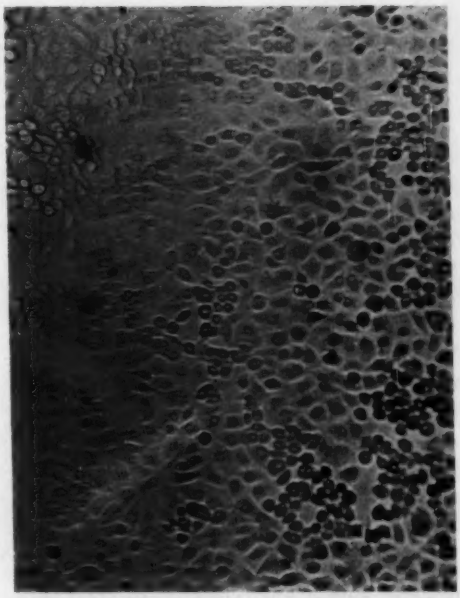
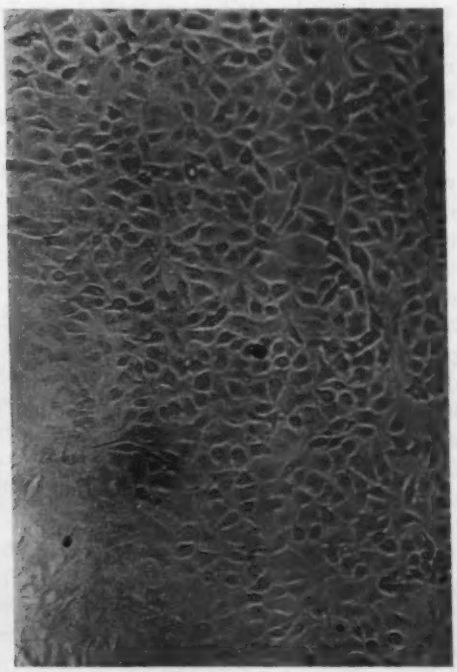


Fig. 2.—The same tube 16 hours after inoculation with herpes simplex. Clusters of rounded refractile cells are appearing.

Fig. 1.—Unstained human amnion roller tube before inoculation. Low power.



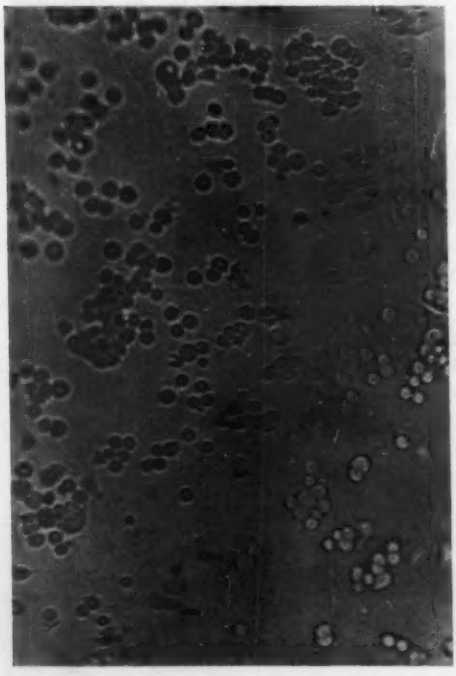
Cells with toxic degeneration were sometimes observed to be round and refractile, but this (1) usually occurred before herpetic changes might be expected and (2) was not observed to begin in discrete foci in an otherwise healthy sheet (as did the herpes) and to progressively enlarge.

Intracellular Changes: In stained sections, characteristic changes may be seen within the cells of herpes-simplex-infected amnion considerably before the grossly visible general cytopathogenic changes are noted. As early as six hours after inoculation there

appear, in hematoxylin-and-eosin-stained preparations, homogeneous very pale blue areas within the nucleus, one to several times the size of the nucleolus. Several of these pale "inclusions" occur within a single nucleus and grow until the chromatin of the nucleus is marginated, the nucleus is gone, and all that remains of the nucleus is a light blue, nearly transparent homogeneous mass with a prominent nuclear membrane. The appearance of the relatively large pale "inclusions" is not accompanied by clumping or appreciable increase in density of the remaining chromatin, and when one focuses on the nucleus the remaining chromatin appears as a fine reticulated structure between these apparently spherical "inclusions" (Figs. 4 and 5).

As changes progress to tissue destruction, nearly all cells are seen to have a pale nucleus, with a fine reticulum of chromatin still seen in many cells. Terminally, the cytoplasm forms a dense eosinophilic clump around the nucleus and seems "pulled away" from the cell membrane, with only occasional strands of cytoplasm extending from the dense perinuclear mass to the cell membrane (Fig. 6).

Fig. 3.—Thirty-six hours after herpes simplex inoculation, the amnion sheet is disrupted and only groups of round cells remain.



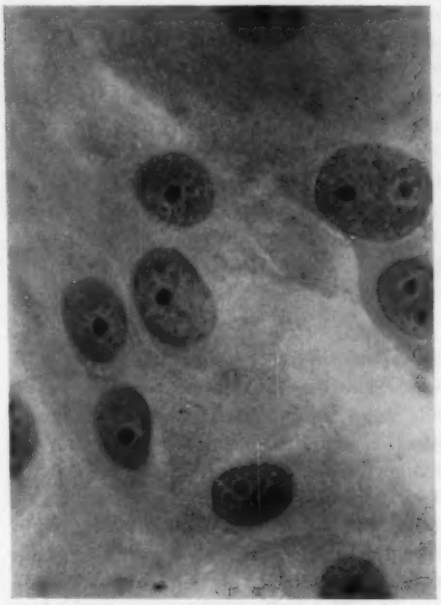


Fig. 4.—Uninoculated stained amnion-cell sheet. High power. Cells are polygonal, and the chromatin is uniformly distributed throughout the nucleus.

Toxic degeneration most characteristically resulted in either pyknosis of the nucleus or, if chromatolysis took place, in the clumping of chromatin in the center of the nucleus and the gradual disappearance of the chromatin. At times, poor staining in a very badly degenerating sheet might cause nuclear pallor superficially suggestive of herpetic degeneration, but the rather large herpetic homogeneous pale areas and the remaining fine reticulum between them were not seen. Cytoplasmic extranuclear vacuoles were surrounded by a dense vacuolar membrane not seen in the nuclear herpetic "inclusions" and were relatively easy to distinguish from the true herpetic degeneration.

Phase-Contrast Microscopy: The observation of the gross clustering of rounded

Fig. 5.—Stained amnion sheet 14 hours after herpes simplex inoculation. The cells are rounded, and many large clear areas appear in the nucleus. The nucleoli are gone. The remaining chromatin is not densely staining, but remains as a fine reticulum between pale areas.

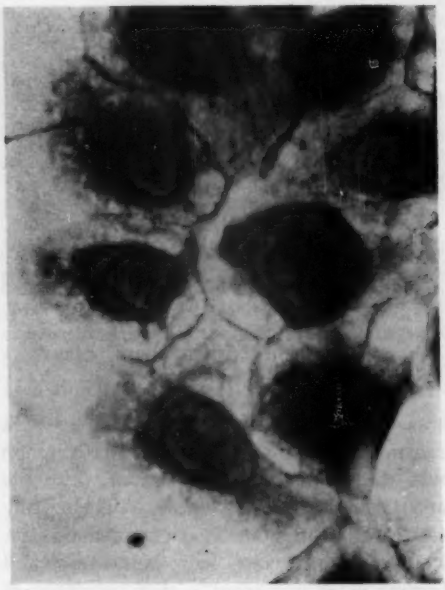
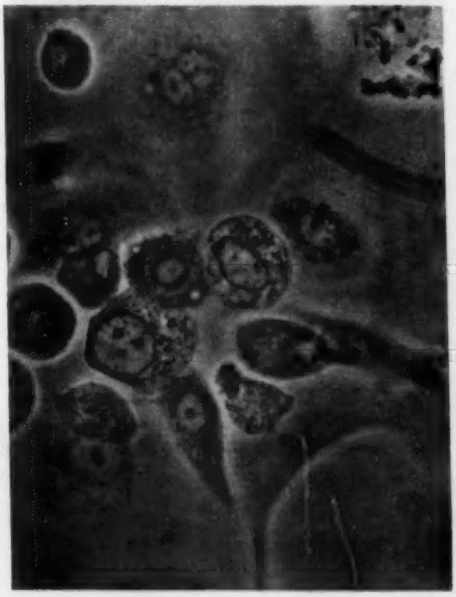


Fig. 6.—36 hours after inoculation, herpes has caused the cytoplasm to form a dense perinuclear ring, leaving the cell periphery clear. Pale areas in the reticulated nuclei are still visible.

Fig. 7.—High-power phase-contrast view of herpes-infected sheet. Note the cells with the pale nuclei and very prominent nuclear membrane.



cells was facilitated by phase-contrast microscopy. In addition, there was a predominance of cells with little or no visible nuclear chromatin and with a very dense nuclear membrane. These nuclear changes were subtle, however, and often difficult to distinguish from other types of degeneration (Fig. 7).

Adenovirus. — General Cytopathogenic Effect: Adenovirus generally produced alterations in unstained tissue sheets within 1 to 7 days after inoculation, though tubes were kept for 14 days, as some changes were delayed.

Two major types of cytopathogenic degeneration were observed: 1. In some types of adenovirus the cells gradually elongated into an arborizing network of cords. This cord formation usually began at the periphery and progressed until the cells sheet

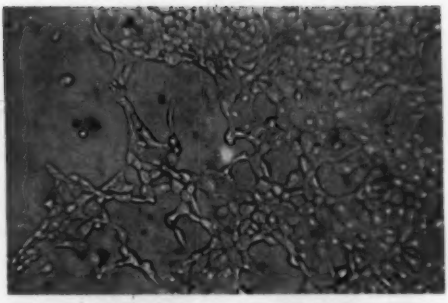


Fig. 8.—Unstained amnion roller tube three days after inoculation with Type 3 adenovirus. The elongated cells form a branching network at the periphery of the sheet.

Adenovirus

Type	Day of Beginning Degeneration	Appearance
1	3	Granular, refractile cells; no cording
2	3	Granular, refractile cells; no cording
3	2	Marked centripetal cording
4	4	Definite cording
5	3	Granular, round cells; no cording
6	3	Granular, refractile cells; no cording
7	3	Definite cording is some tubes, but a few tubes showed refractility with no appreciable cording
8	8	Cording, but not marked
9	7	Definite cording, but in the periphery and center of the sheet
10	4	Definite centripetal cording
11	8	Cording, but not marked
12	5	Definite cording, slight

was totally disrupted and only a network remained (Figs. 8 and 9). 2. More common was the gradual development of refractile and granular cells. These cells, usually scattered at random throughout the sheet, were not in discrete foci or clusters, and became more numerous with time. Though less polygonal than normal, adenovirus-infected cells did not form the perfectly round cells seen with herpes simplex. Some adenovirus (for example, Type 7) produced both types of change, sometimes one being more prominent than the other.

A more detailed study of possible type-specificity of adenovirus cytopathogenic effects is in progress; preliminary results are summarized in the Table.

Intracellular Changes: The first cytopathogenic effects generally noted were the appearance of small pale areas in the nucleus about the size of a nucleolus, vacuolization of the cytoplasm peripherally, the gradual clumping of chromatin, and the appearance of nuclear basophilic bodies indistinguishable from the nucleolus (Fig. 10).

Following this, there was distortion of the nucleus and clumping of chromatin to form punctate or dense, irregular, large, basophilic bodies, sometimes with honey-combing of the nuclear mass. Eosinophilic inclusions, though sometimes present, were not a constant or a diagnostic finding. The cytoplasm sometimes condensed as an irregular

Fig. 9.—Stained amnion coverslip three days after Type 3 adenovirus inoculation. In addition to the arborization and variety of cell size, multiform nuclear configurations may be noted.

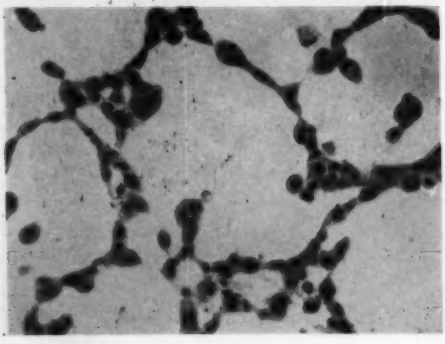


Fig. 10.—Type 8 adenovirus three days after inoculation into amnion. In this stained section early degeneration is shown by the appearance of cytoplasmic vacuolation, the small clear areas within the nucleus, and the dense staining of the remaining chromatin as compared with the normal cells.

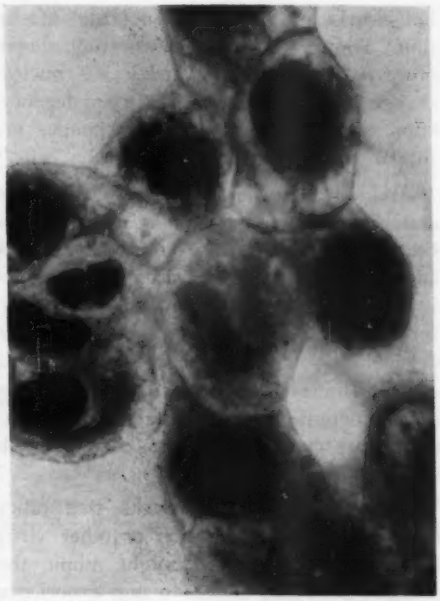


Fig. 11.—Type 3 adenovirus three days after inoculation. High power. Some of the many types of more advanced adenovirus nuclear degenerations are seen. The variety of densely basophilic nuclear masses is readily appreciated, but the eosinophilic inclusions present in the large pale central cell are difficult to see.

and deeply staining mass around the nucleus, but cytoplasmic alterations were not always seen (Fig. 12). These cellular changes were similar to those described for HeLa cells,[11,12] (Figs. 9 to 12).

The variety of cellular alterations may be illustrated by the description below of a single amnion slide infected with 0.1 ml. of adenovirus Type 3, observed 25 hours after inoculation (Fig. 11).

"Most cells showed clumping and condensation of the chromatin. In many cells there was seen a dense basophilic intranuclear mass which was either round, horseshoe-shaped or star-shaped and sometimes appeared honey-combed. These nuclear masses were surrounded by a clear homogeneous zone traversed only by rare basophilic strands.

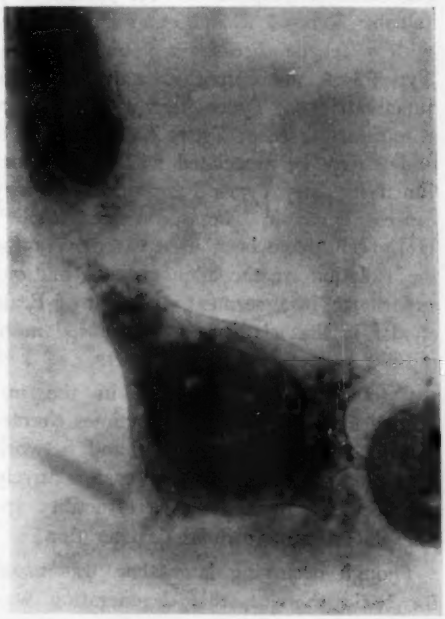
"In some cells the nuclei were several times normal size. In some, the nuclei, instead of containing a dense blue mass, contained punctate basophilic material, either in a single large area, in smaller discrete areas, or in an arborizing pattern. Eosinophilic inclusions, from 1 to 10 in number, appeared within the nuclei, sometimes immediately surrounded by blue chromatin, and sometimes with a space between chromatin and inclusion."

Though any description of such a variety of patterns is necessarily confusing, the early formation of the small clear nuclear areas and the subsequent dense irregular basophilic nuclear masses was very definite and difficult to mistake, and the heterogeneity of nuclear appearance, in itself, was characteristic.

Phase-Contrast Microscopy: Though this facilitated the observation of general tissue changes and cytoplasmic vacuolation, intracellular changes were more readily observed by staining.

In our hands, observation was most satisfactory when "flying coverslips" were used and staining was done at the time that

Fig. 12.—Type 8 adenovirus showing a dense nuclear mass, with the surrounding cytoplasm forming a heavy perinuclear crescent.



cytopathogenic changes were noted in the unstained specimens.

Comment

Although many methods have been described for the isolation of herpes simplex virus,[7-9,15] few provide a convenient method that will also permit the detection of other important viruses, such as the adenoviruses. The question of whether virus isolation indicates causative infection will not be considered, but the desirability of isolation and identification of the virus both for diagnostic and for epidemiological purposes is undisputed, and human amnion tissue culture provides a rapid simple method.

The changes produced in human amnion cells in tissue culture by herpes simplex develop promptly (as early as six hours) and are quite characteristic, especially if both the gross alterations in the unstained tissue sheet and the cellular morphology of stained specimens are observed.

The adenoviruses were first isolated by Rowe et al. in 1953,[16] and not until 1956 was the present method of nomenclature and classification adopted.[17,18] At present it is felt that Types 1, 2, and 5 may be associated with a febrile disease in young children; Types 3, 4, and 7 may cause pharyngoconjunctival fever; Type 4 may cause an acute respiratory disease; Types 2, 3, 4, 5, 6, 7, 8, and 9 may be associated with simple conjunctivitis, and Types 8 and perhaps 3 may cause epidemic keratoconjunctivitis.[19-23] HeLa cells have been used extensively for the isolation of the adenoviruses, but our experience, in agreement with that of Beale et al.,[9] is that changes are produced more rapidly in amnion-cell monolayers.

Cytopathogenic alterations in the unstained tissue sheet were sometimes characteristic consisting of cording and network formation. More often, however, a relatively nonspecific granularity and refractility appeared, indicating cellular degeneration.

Though occurring later than was usual for toxic changes, this degeneration was not clearly specific for adenovirus infestation. Staining of the degenerating sheets, however, revealed a variety of nuclear changes that were not seen in toxic degeneration of amnion cells. These changes are similar to those described in HeLa cells.[13]

Amnion cells are convenient, inexpensive, and easily maintained. Cytopathogenic changes from infection by herpes simplex and adenovirus are characteristic and develop rapidly. An optimal method for observing these changes was to watch the degeneration in a cell sheet growing on a coverslip or roller tube, and, once changes became definite, to fix and stain the preparation, thus correlating gross changes with microscopic appearance.

While the possibility exists that other types of toxic degeneration or other virus infestations not studied might mimic the changes described above, in our experience these changes were specific, and very easy to identify.

The relative ease of tissue preparation and the ease of detection of cytopathic changes make this an excellent tissue for the isolation of these ocular viruses—especialy for a routine diagnostic laboratory of moderate size.

Summary

Human amnion-cell tissue culture provides a simple and convenient method for virus isolation. The cytopathogenic changes caused by herpes simplex and adenovirus develop rapidly, appear to be characteristic and are easily identified and differentiated from nonspecific degeneration if both stained and unstained preparations are observed.

The convenience of the method and the ease of virus identification make this method an excellent tool for the routine isolation of these ocular viruses, easily adapted to the laboratory of moderate size.

Dr. Sidney Kibrick provided advice and guidance and also "stock" viruses and amnion tissue. Dr. D. G. Cogan provided laboratory facilities.

Ophthalmology Branch, National Institute of Neurological Diseases and Blindness (14).

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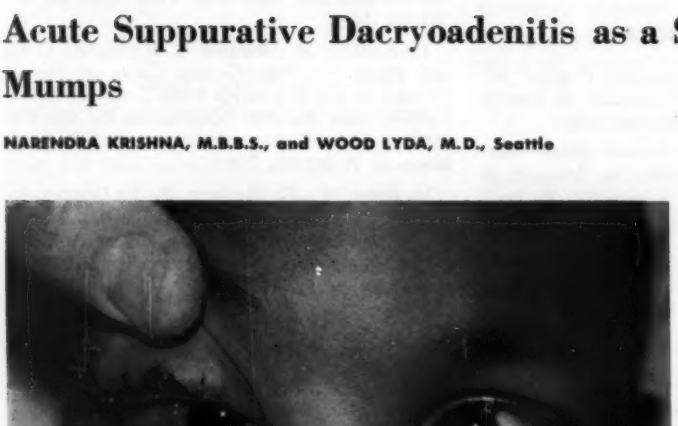
Acute Suppurative Dacryoadenitis as a Sequel to Mumps

NARENDRA KRISHNA, M.B.B.S., and WOOD LYDA, M.D., Seattle



Acute suppurative dacryoadenitis, showing displacement of the eye and the enlarged suppurative area in the upper lid.

Acute dacryoadenitis is a relatively rare condition usually caused by the mumps virus. According to Duke-Elder [1] the dacryoadenitis of mumps is always bilateral and nonsuppurative. The case we are presenting is somewhat unusual in that the dacryoadenitis occurred as the symptoms of mumps were subsiding and it was unilateral and suppurative. Duke-Elder [1] feels that suppurative dacryoadenitis occurs only with systemic infection, presumably bacterial. In this patient there was no positive systemic finding except a positive complement-fixation test to the virus of mumps.

Report of a Case

A 6-year-old Negro boy was admitted to King County Hospital, Seattle, Nov. 7, 1955. The chief complaint was of an increasing pain, tenderness, and swelling of the lateral portion of the left upper eye lid for three days.

Two weeks prior to admission the patient had been sent home from school, where the incidence of mumps had been high, with malaise, nausea, abdominal tenderness, and pain behind the left ear. For the next four days there was pain, swelling, and tenderness over the parotid gland as well as a high fever. The symptoms and signs of an acute parotitis were gradually subsiding when the left eye lid became swollen and tender.

Examination of the left eye on admission showed a red, full, and tender left upper lid (Figure). When the upper lid was everted, a swollen, red, and tender lacrimal gland about the size of an almond was prolapsed into the upper conjunctival fornix. Both palpebral and bulbar conjunctivæ were injected and chemotic. The eye was

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displaced medially and inferiorly. No mass could be palpated in the lacrimal area of the right eye. The fundus and other structures of both eyes were normal.

The orifices of the parotid (Stenson's) ducts showed a mild erythema. Both parotid glands were slightly swollen and tender. The submaxillary glands were swollen but nontender. No signs of involvement of the central nervous system or of the testes could be found.

The blood studies showed a hematocrit value of 41%; 6000 white blood cells, with a differential count of 51% segmented cells, 27% lymphocytes, 20% monocytes, 1% eosinophils, 1% basophils, and 0.2% reticulocytes. The corrected sedimentation rate was 28 mm. in an hour. The serology was nonreactive, and the alkaline phosphatase was 10.7 units. Urine, stool, and P. P. D. No. 1 studies were negative. The cerebral spinal fluid was clear, under normal pressure, and laboratory studies showed two cells, negative bacterial culture, and 19 mg. of protein per 100 cc. Conjunctival cultures made at the time of admission had a light growth of coagulose-negative Micrococcus pyogenes var. aureus sensitive to all of the sulfonamides and antibiotics tested. No Gram-negative organisms were present.

Mumps antigen tests showed a 1:64 titer in the acute-phase specimen and a 1:64 titer in the convalescent-phase specimen. The mumps complement-fixation test was heterophile-positive, 1:7, compatible with a recent mumps infection. A careful survey for tuberculosis was negative.

The patient was treated with local sodium sulfacetamide-chlortetracycline (Aureomycin) ointment, hot boric acid compresses, and systemic supportive therapy. The area over the lacrimal gland increased in redness, size, and tenderness and became fluctuant. The mass was aspirated, and approximately 2 cc. of a milky material was obtained that was negative to bacterial culture. After 48 hours the gland was again swollen and tender, and so the mass was incised and a rubber drain was inserted into the incision. The milky exudate obtained was again negative to bacterial culture. Tissue removed at the same time showed glandular structures infiltrated with lymphocytes and leukocytes.

The patient made an uneventful recovery and was discharged from the hospital on Nov. 22, 1955. A follow-up of the case one year later showed no abnormalities in tear formation, in position and movement of the globe, or in the fundus.

Comment

Acute dacryoadenitis occasionally occurs with mumps as a bilateral nonsuppurative swelling. The case we have presented is of interest in that an acute unilateral suppurative dacryoadenitis appeared in a serologically confirmed case of mumps.

An intense survey for systemic infection other than mumps was made in an attempt to rule out a systemic infection as a source of the suppurative dacryoadenitis. Repeated bacterial cultures of the exudate from the glands were negative, and no other source of infection could be found in the nose, throat, or other systems.

Medical and Dental Bldg. (1) (Dr. Lyda).

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Electronic Pupillography

A New Instrument and Some Clinical Applications

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Pupillary reactions have been studied for centuries. Their use in physiological research as indicators of autonomic nervous activity dates back to the 18th century (du Petit, 1727 [1]), and the interest of physicians, to a much earlier period (Galen). This interest was intensified during the 19th century. Horner's description of the effects of peripheral sympathetic lesions in man (1869 [3]), Argyll Robertson's discovery of the syndrome which bears his name (1869 [4]), and numerous other reports on pupillary behavior under normal and pathological conditions stimulated and sustained it.

Unfortunately, accurate observation of pupillary reactions is difficult. The smallness of the pupils, the swiftness of their motions, the impossibility of observing the patient's two eyes simultaneously, and the changes in pupillary behavior under different experimental conditions are some of the factors contributing to this difficulty. For these reasons, many methods of pupillary measurement have been developed in the course of time. These methods can be grouped roughly as follows: (1) entoptic methods, in which the patient himself determines the pupillary diameter; (2) methods in which the observer measures the patient's pupillary diameter by direct observation, with the aid of lenses, scales, mirrors, prisms, telescopes, and other optical devices; (3) functional methods, such as the determination of the threshold of pupillary reactivity, of the reaction time, or of other functions; (4) photographic methods, furnishing a permanent record of the pupillary size; (5) dynamic methods, furnishing a permanent record of the pupillary movements.

None of these methods was satisfactory in practice. Some of them furnished inaccurate results and served merely to confuse the already complicated controversies in the literature. Others were extremely time-consuming.

"Pupillography," in the currently used sense of the term, was introduced by one of us (O. L.) about 30 years ago. It belongs to the last group of methods (Category 5). It consists of the accurate recording and detailed analysis of the pupillary movements of the two eyes under controlled conditions of light and darkness.* The pupillographic method was developed during the following decades, in step with the advances of modern technology.[5-12] Briefly described, the pupillographic technique routinely used in this laboratory for clinical cases up to 1957 involves two separate procedures.

1. Motion pictures (film speed usually 10 frames per second, up to 50 per second in special experiments) are taken of the patients' two eyes in dark red-infrared illumination † while the pupils contract and dilate in response to various stimuli. To conserve film, the camera mechanism was

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* Earlier methods were limited to the registration of pupillary movements in light only.

† Prior to 1935, blue light was used, with tangential arrangement of the light sources.

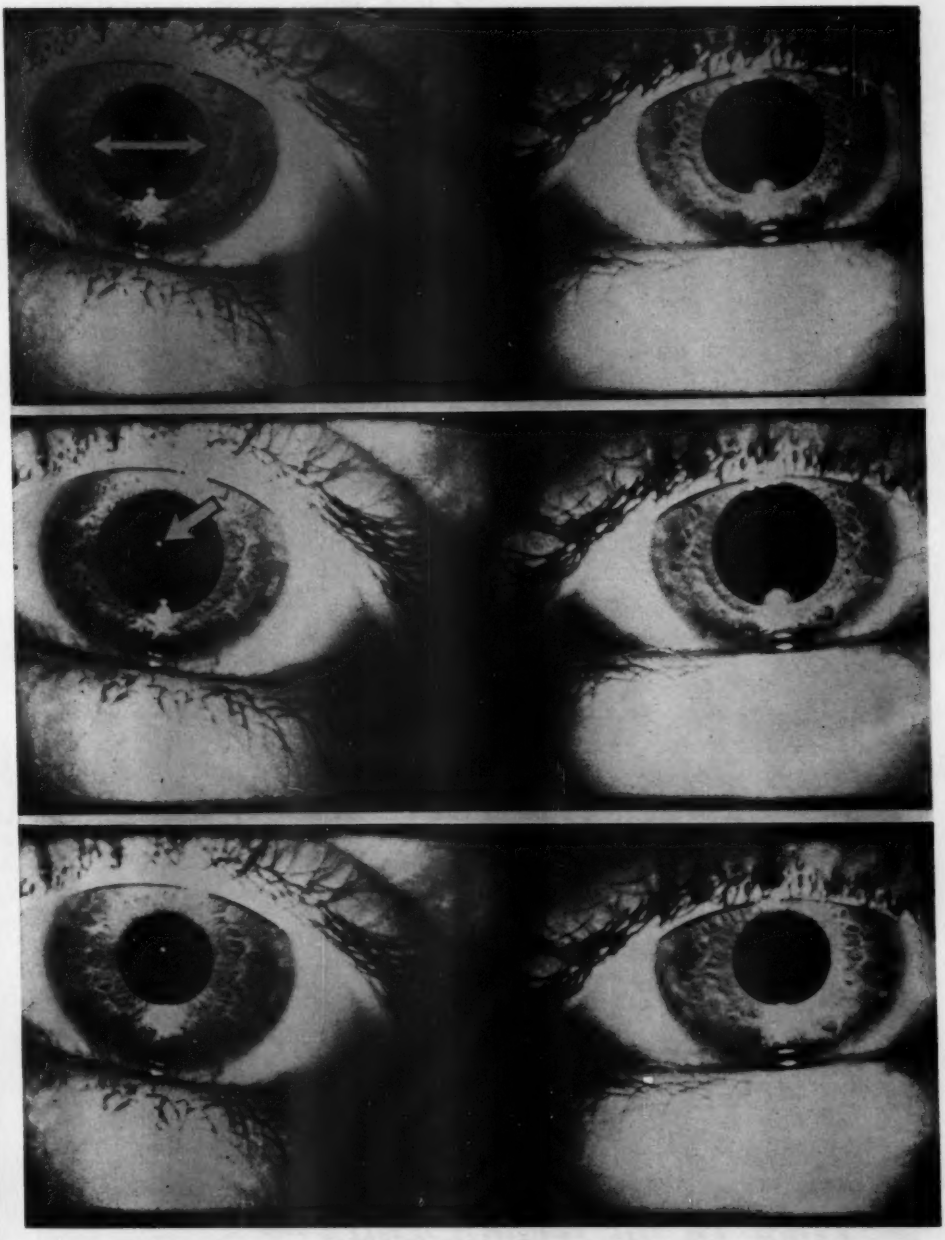

Fig. 1.—Photographic enlargements, obtained from a pupillographic film negative. Since the camera mechanism has been altered to transport the 35 mm. film in half-frame steps, each single image measures about 24×9.5 mm. By means of a double-lens system, the patient's two eyes are made to appear directly side by side, their temporal edges adjoining, while the space ordinarily occupied by the bridge of the nose is eliminated. For pupillographic measuring, the largest horizontal pupillary diameter is used (indicated by the double arrow). Upper picture: In dark red-infrared illumination, the pupils are large. The corneal highlights on the lower edge of the pupil are caused by the infrared illumination. Middle picture: first frame (0.1 second) after the beginning of stimulation by green-yellow light on the left side. The arrow points to the corneal highlight of this stimulating light. The pupil has not yet begun to contract (latency period about 0.2 second). Lower picture: 0.8 second later; both pupils have contracted.

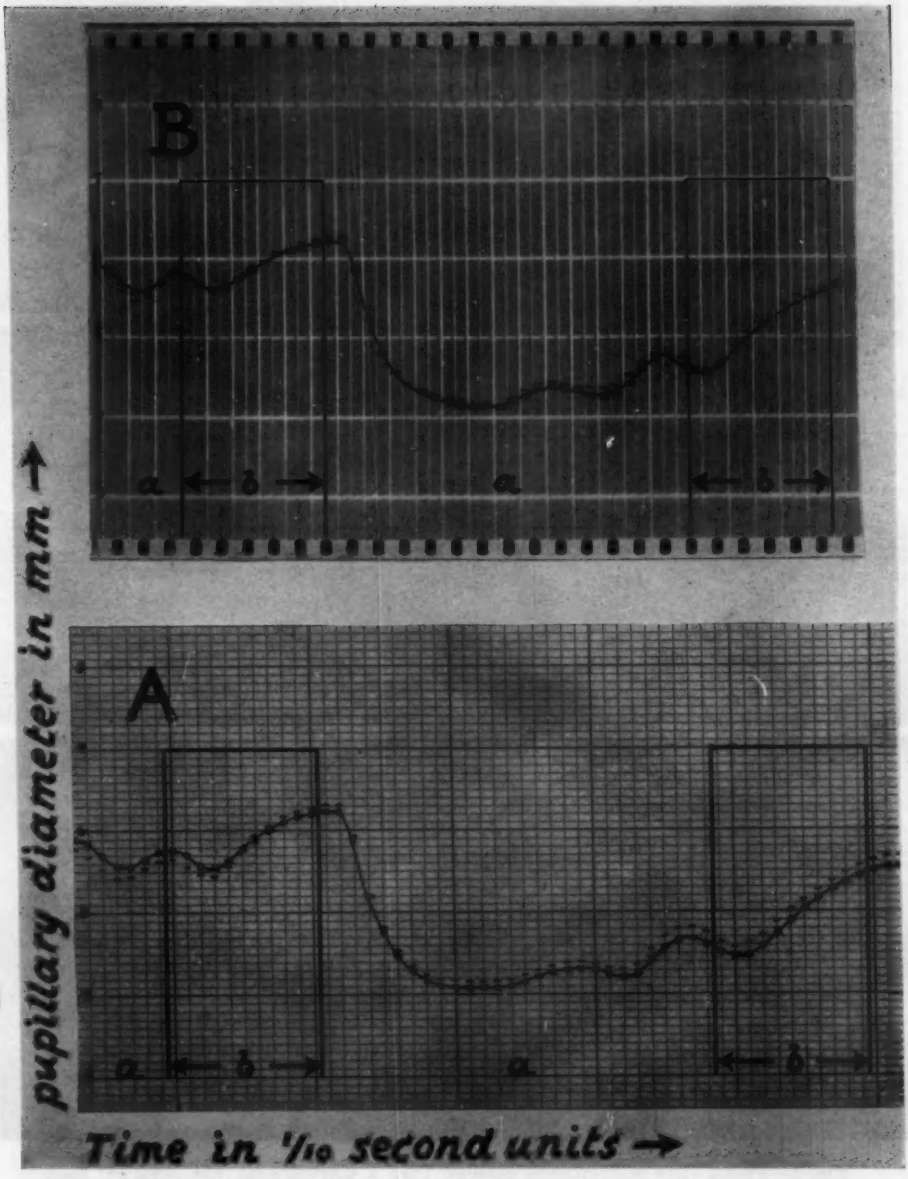

Fig. 2.—Pupillogram of two reactions to darkness. In *A* (lower line) the pupillary diameter has been measured by hand, with the aid of measuring calipers. Each cross represents a measurement of the right pupil; each small horizontal line, that of the left pupil. In *B* (upper line) the measurement was done by the oscillographic scanning method and recorded on photosensitive paper. In each graph the curve for the right pupil has been drawn with pen and ink. (*a*) The patient's eye is adapted to light; (*b*) the light is interrupted.

altered to transport the film in half-frame steps. Since 1946 a double lens system has been used which makes it possible to place the images of the right and the left eye side by side on the film, their temporal edges adjoining (Fig. 1.) The film space ordinarily wasted by the bridge of the nose can thus be used for the eye images, photographed at one-half natural size.

2. The negative film images are enlarged by projection, and the largest pupillary diameter is measured for each picture. The values thus obtained are plotted as the ordinate, against time as the abscissa, in a coordinate graph (Fig. 2.).

Up to 1947, these measurements were done by hand, with the aid of measuring calipers. Since a routine clinical film required 4000 individual measurements, this method was time-consuming. Moreover, skilled and conscientious personnel were needed for accurate measurements. During the years 1943-1947, therefore, an electronic measuring instrument was developed in this laboratory.

With use of the pupillographic film negative, the projected images of the eyes were scanned by a rotating mirror over a slit mask which covered a photocell. The time needed for the pupil portion of each of the images to scan over the slit mask was measured by an oscilloscope and recorded photographically on a paper strip.

Although this instrument worked relatively fast and with high precision (Fig. 2), the process was too complex for general clinical use. In addition, operating costs were high because of the large amounts of infrared-sensitive film needed. Therefore, an electronic direct-writing instrument was developed during the years 1953-1957. This instrument is the chief subject of this report.

A. Principle of the Method

Basically, two electronic measuring methods were possible. (1) The patient's eye could be illuminated from a steady source, and the light reflected by the eye could be recorded photoelectrically, whereby the expanding and contracting black pupil would cause a greater or smaller deflection on the measuring instrument, or (2) the time consumed by scanning the largest diameter of the pupil could be measured.

Measurement of the reflected light would have been relatively simple and inexpensive. However, the problem of variations in optical conditions from patient to patient is encountered in such measurements. The infrared light reflected by the iris portion of the eye rises with the amount of pigment in the iris, while the light reflected from the pupil portion changes inversely with the pigmentation of the eye. Therefore, when a photoelectric pick-up device sensitive in the infrared region of the spectrum is used, an actual pupillary expansion or contraction of a given amplitude will give different readings for a blue and for a brown eye. According to our measurements, this error can exceed 60% of the total reading.

For this reason, and because of other shortcomings of photometric measuring systems,[13] we decided to base our system on the measurement of the scanning time.

B. The Electronic Pupillograph: Its Working Principles

The first method, developed during 1953-1955,[14] was based on a modified closed-circuit television system. This method was abandoned mainly because certain characteristics of the infrared-sensitive pick-up tube rendered the system unduly complex if the required sensitivity and accuracy were to be achieved.

During 1956, an instrument was constructed by the General Precision Laboratory, Inc., of Pleasantville, N. Y., with our collaboration.‡ For the following description of the instrument and its use, see Figures 3-8.

A tungsten light source (Fig. 3, *a*) is placed in the center of a rotating drum (*b*). A condensor lens (*c*) collects a beam of light which passes through slits in the wall of the rotating drum (*d*) and through an

‡ Dr. Frank Gillette, Mr. George King, and their collaborators made this development possible.

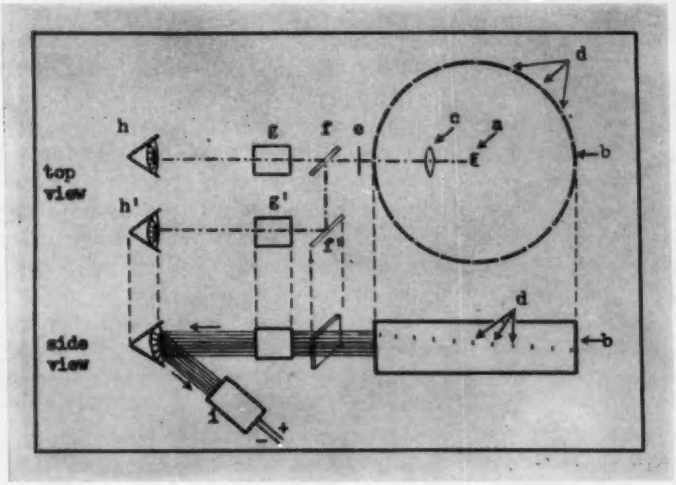

Fig. 3.—Diagram of the electronic scanning method. (*a*) Tungsten light source; (*b*) rotating drum; (*c*) condensing lens; (*d*) slits in the wall of the rotating drum; (*e*) infrared filter; (*f*) semitransparent mirror; (*f'*) total reflecting mirror; (*g*) and (*g'*) optical systems which form the images of slits (*d*) at the level of the eyes (*h*) and (*h'*); (*i*) infrared-sensitive photocell. (See Section B of the text.)

infrared filter (*e*). A semitransparent mirror (*f*) divides the beam. The transmitted portion is used to measure the left pupil, while the reflected portion is picked up by a total-reflecting mirror (*f'*) for the measurement of the right pupil. A matched pair of lenses (*g* and *g'*) form the images of the scanning slits at the level of the patient's eyes (*h* and *h'*). The light reflected by each eye is picked up by an infrared-sensitive phototube (*i*).

Each of the scanning slits on the drum is cut at a slightly lower level than the preceding one (Fig. 3, side view, *d*). The

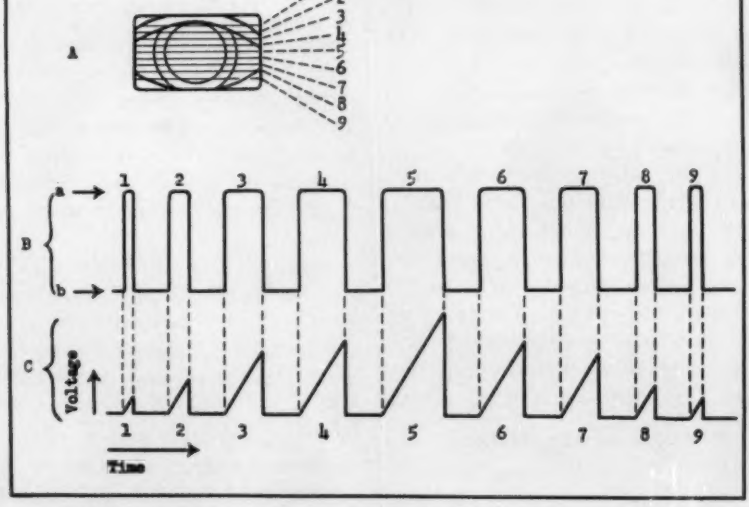

Fig. 4.—Electronic signals derived from scanning the eye. *A* shows a diagram of the human eye. Some of the electronic scanning lines are indicated by numbers (*1-9*). In *B*, the electronic pulses corresponding to the scanning lines *1-9* are shown; (*a*) indicates the "black"; (*b*), the "white" levels of the signal. In *C*, the square-wave pulses of *B* have been converted to triangular shape, whereby the duration of the pulses in *B* controls the amplitude of those in *C*.

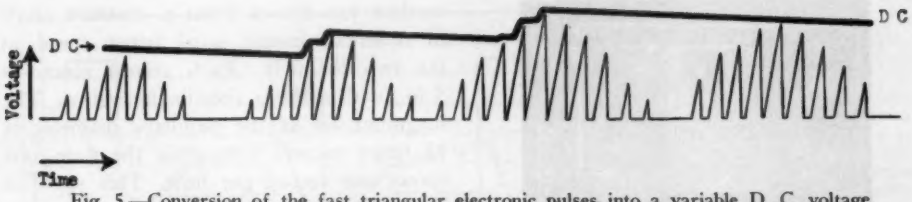

Fig. 5.—Conversion of the fast triangular electronic pulses into a variable D. C. voltage. The D. C. voltage cannot follow the fast triangular waves but instead "rides on top" of the largest triangular signals, i. e., it follows the largest horizontal pupillary diameter.

vertical position of the scanning light spots on the eye therefore varies, and when the drum rotates, each single rotation causes a set of overlapping light spots to scan the eye.

As long as these scanning light spots fall on the iris area of the eye, a large portion of the light is reflected and is picked up by the phototube; but when the scanning spots enter the pupil portion of the eye very little light is reflected on the phototube. The phototube, therefore, emits a high level of signal-voltage ("white") during the iris portion of each sweep and a low signal-voltage ("black") during the pupil portion of each sweep (Fig. 4, *A* and *B*).

One scanning spot of each set crosses the pupil at its largest horizontal diameter (No. 5 in Fig. 4, *A* and *B*). These largest-diameter scans are made to control the measurement in the following way: (*a*) The square "white-black" impulses furnished by the phototube (Fig. 4, *B*) are converted into triangular pulses (Fig. 4, *C*), whereby the duration of each square-wave pulse controls the amplitude of each triangular pulse. (*b*) Diode peak detector circuits are used to "demodulate the envelope" of these triangular sets of pulses, i. e., they convert the triangular pulses into a variable D. C. potential which follows the largest triangular pulses (Fig. 5). (*c*) The D. C. potential for each eye can then be directly recorded.

C. Details of the Instrument and Its Use

An ordinary gray metal desk is used to contain most of the electronic parts (Fig. 6, *A*). The scanning unit (*B*) is supported by a crane-like structure (*C*), which allows horizontal and vertical adjustments. A chin rest and headrest (*D*) are attached to the scanning box. For fixation of the gaze at far vision, the patient sees a small, dark-red light at a distance of 36 in. This light

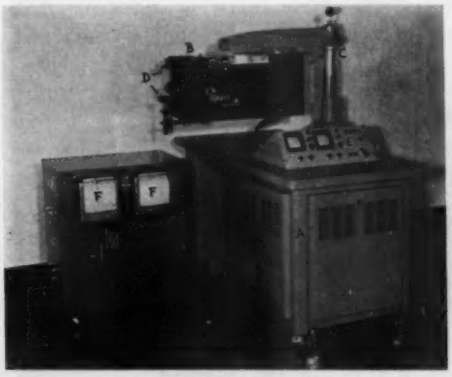

Fig. 6.—Photograph of the electronic pupillograph. The cover of the scanning box has been removed to show some of the working parts. *A*, main desk; *B*, scanning box; *C*, crane support; *D*, chin- and headrest; *E*, control panel, with two oscilloscope tubes and controls; *F*, recorders; *G*, recorder cabinet.

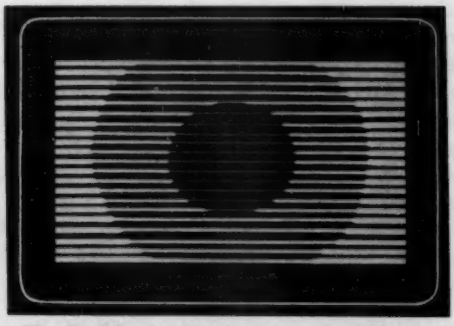

Fig. 7.—Diagram showing the scanned image of the eye. The scanned images of the right and left eyes can be observed on the oscilloscope tubes of Figure 6,*E*. They are used for optical alignment and focusing.

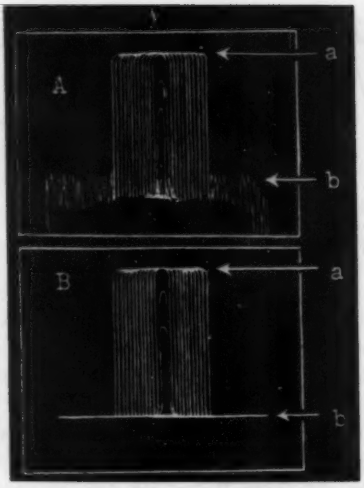

Fig. 8.—Electronic signals and adjustment. The electronic square-wave signals can be examined on the oscilloscope tubes of Figure 6,*E*. In *A*, the "black" pupil (*a*) and "white" iris (*b*) portions of the signals are shown. In *B*, the iris signal has been clipped off, leaving a group of essentially square signals. The width of the entire group, equivalent to the largest horizontal pupillary diameter, is converted into a variable D. C. voltage and then recorded.

is presented by means of a mirror arrangement inside the scanning box. When the near-vision reaction is to be elicited, an optical system substitutes a near target (4 to 12 in. distance, variable) for the "far point."

A control panel (*E*) contains two 3 in. oscilloscope tubes as well as controls for adjusting the signal. In the "picture" position of a master switch, the scanned images of the eyes can be seen, as shown in the diagram of Figure 7. After proper alignment and optical focusing, the electronic square-wave pulses can be examined. The gain of the signal is adjusted until the "black" and "white" levels of the signal reach a predetermined position, as shown in Figure 8*A*. By means of clipping circuits, the iris portion of the pulses is suppressed, and the signal appears as in Figure 8*B*.

The final D. C. measuring potentials are recorded on two recorders, one for each eye (Fig. 6, *F*). They are mounted in a separate cabinet (Fig. 6, *G*). The two recorders are driven from a common shaft in order to insure equal paper speed in the two channels. Each record measures 5 in., with a linear coordinate system. The magnification of the pupillary diameter is 15 times natural size, while the time axis shows one second per inch. This speed is routinely used, since the smooth-muscle reactions of the iris are relatively slow. If higher speed is desired, for example, when the reactions of the striated bird iris are to be recorded, an oscilloscopic recording system could be substituted for the direct-writing recorders. Event markers are used to coordinate the traces and to record moments of elicitation of visual and of other stimuli.

The accuracy of the instrument is high. For periodic tests, a series of drill holes in a black plastic strip are used (approximate infrared-reflectivity of the human eye). The strip is clamped into proper focusing position and target holes of 2, 4, 6, 8, and 10 mm. diameter are measured in succession. Under these experimental conditions, the approximate accuracy of the instrument can be defined as follows: (*a*) stability, error ±0.5%, for weeks; (*b*) over-all linearity, 99%; (*c*) measurement in terms of absolute pupillary size, set by calibration of the instrument and therefore asumed to be correct; (*d*) ability to follow small pupillary oscillations, 0.025 mm. pupillary diameter or less; (*e*) "dead space" of the recorder, less than 0.25% full scale; (*f*) channel equality, since virtually no interdependence of the two channels exists, this value depends only on the absolute accuracy and linearity of the two channels.

Figure 9 shows the pupillogram of three successive reactions to light, measured by the new electronic pupillograph.

D. Some Clinical Applications of the Method

The purpose of clinical pupillography is the detection and localization of pathological processes within the nervous centers and pathways of pupillary control. Under a

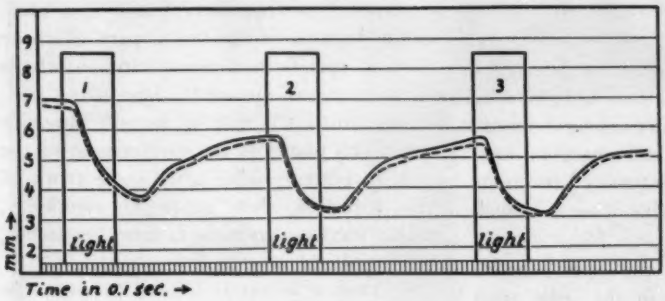

Fig. 9.—Three reactions to light in a normal subject. The original pupillograms of the right and left eyes, recorded by the electronic pupillograph, are superimposed.

given set of experimental conditions, the normal pupillary reflexes conform to a definite pattern. But when a lesion disturbs one of the neurones of the reflex arcs for pupillary contraction or dilatation the physiological reflex pattern is characteristically modified. In other words, lesions at specific sites within the nervous centers and pathways of pupillary control cause specific changes in the pupillary reflex pattern.

In Figure 10 the parasympathetic reflex arc is shown. The lesions most commonly encountered in practice are indicated, and the pupillary syndromes resulting from such lesions are shown.

1. Complete destruction of the receptor organs in the retina or interruption of the optic nerve obviously results in absence of the pupillary reflex to light, when the eye on the side of the lesion is stimulated. Both pupils react normally when the normal eye is exposed to the light stimulus. It is important to note that such lesions—unless complicated by other pathology in the sympa-

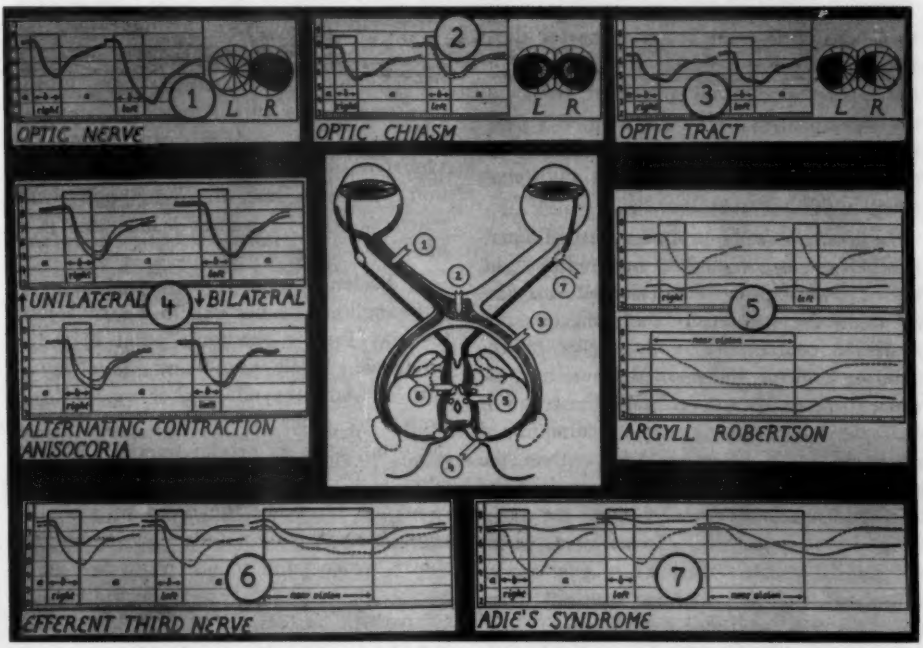

Fig. 10.—Clinical lesions in the parasympathetic reflex arc. The numbers *1-7* indicate the lesions most often encountered in practice. The corresponding pupillograms *1-7* show changes in pupillary reactions caused by these lesions. For details, see Section D of the text.

thetic or parasympathetic supply of the iris —do not cause inequality of the pupils.

Partial lesions of the retina or optic nerve cause "low-intensity" reactions to light, i. e., the pupil reacts to high-intensity light stimuli as the normal pupil would react to low-intensity stimuli. "Low-intensity" reactions are rather slow, inextensive, and w-shaped (Fig. 10, *1*).[11]

2 and 3. Lesions in the optic chiasm (Fig. 10, *2*) or lesions in the optic tract (Fig. 10, *3*) cause "low-intensity" light reactions to appear when either eye is stimulated by bright light. The visual field, of course, is different in the two conditions. "Low-intensity" reactions are sometimes found in cases of multiple sclerosis after an episode of retrobulbar neuritis, though the visual fields have become normal. In such cases, "low-intensity" pupillary reactions may be the only objective sign to make certain the existence of multiple sclerosis when transitory blindness in the patient's history points to this possibility.[11,15]

4. The pupillary light reflex pathways leave the optic tract at its posterior third. From this point on, the visual path continues to the external geniculate body and the occipital lobe, while the pupillary pathways descend to the midbrain. Therefore, pathological pupillary reactions no longer coincide with visual defects.

In normal man both pupils contract equally when one eye alone is stimulated by light, but in cases with lesions in the anterior dorsal midbrain, specifically the pretectal area, posterior commissure, and brachia of the anterior colliculi, the pupils become unequal when the eyes are unevenly illuminated. For example, when the right eye is illuminated the right pupil becomes smaller than the left, and when the left eye is stimulated the left pupil becomes smaller than the right (Fig. 10, *4*, lower line). In unilateral cases the pupils remain equal when one eye is stimulated, but they become unequal when the other eye is stimulated (Figure 10, *4*, upper line). This syndrome, named by one of us (O. L.) "alternating contraction anisocoria," is frequently found in a number of diseases of the brain, particularly in cases of specific and nonspecific infections of the nervous system.[16] Alternating contraction anisocoria may be the only objective sign which points to the involvement of the brain in patients who, after some types of virus infection, show unspecific symptoms, such as increased general fatigue, headaches, and peripheral neuritis.[17]

5. When a lesion is located between the pretectal area and the Westphal-Edinger nucleus, close enough to the nucleus to interfere with both the crossed and the uncrossed pretectal fibers, a unilateral or bilateral Argyll Robertson pupil may develop (Fig. 10, *5*). In cases with larger lesions, which also involve the fibers for pupillary contraction to near vision, complete immobility of the miotic pupil results.[18,19] The Argyll Robertson pupil, long considered an unfailing symptom of syphilis of the central nervous system, is actually, like all other pupillary symptoms, merely an indicator of the localization of a lesion. This lesion is often, but not always, syphilitic in origin.

6. Lesions in the third-nerve nucleus or the efferent parasympathetic path lead to mydriatic pupils with reduced or absent reactions to light and to near vision. This syndrome differs from alternating contraction anisocoria, since the same pupil always reacts poorly, no matter which eye is illuminated (Fig. 10, *6*).

7. Lesions in the ciliary ganglion or its postganglionic connections to the iris sphincter may lead to the tonic pupil of Adie's syndrome. While pupillotonia is always a part of Adie's syndrome, it may also be caused by other pathological processes in the orbit, such as orbital tumors (Fig. 10, *7*).[19,20]

Figure 11 shows the brain in a sagittal view. A number of pupillary syndromes are shown which point to lesions in the supranuclear diencephalic centers or the efferent sympathetic system.

1. Lesions in the peripheral sympathetic system, either preganglionic of postgan-

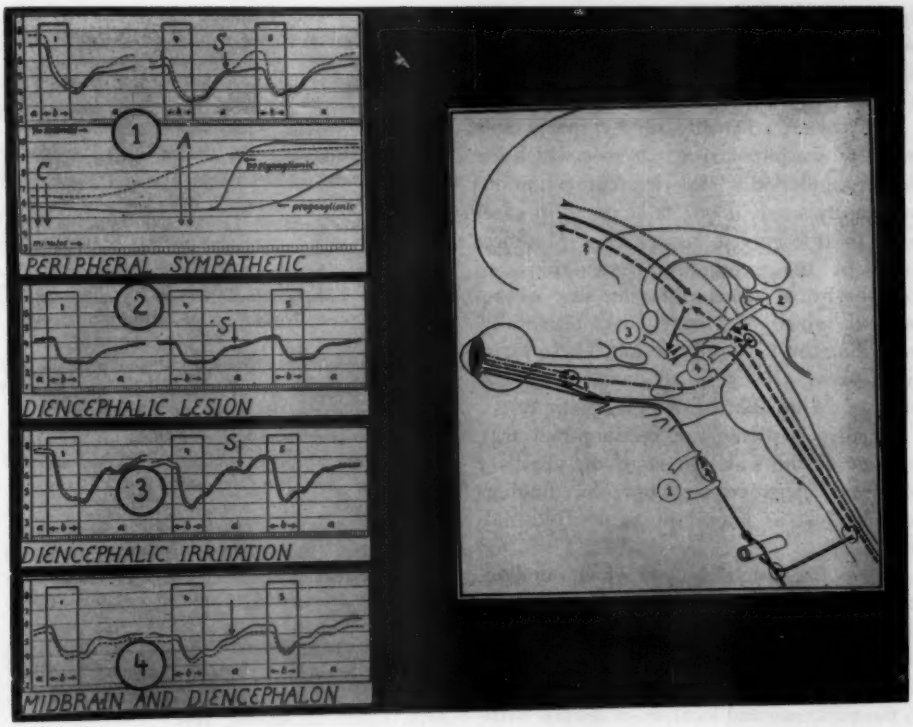

Fig. 11.—Clinical conditions of the supranuclear diencephalic centers and the efferent sympathetic system. The brain is shown in a midsagittal view. The lesions *1-4* correspond to the pupillograms *1-4*. For details, see Section D of the text.

glionic, cause pupillary inequality which persists in darkness, decreases in light, and increases under the influence of psychosensory stimulation. In addition, the pupil on the side of the lesion fails to dilate to conjunctival instillations of cocaine hydrochloride (2%), while it shows an exaggerated dilatation upon additional instillation of epinephrine chloride (1:1000; Fig. 11, *1*).[21]

Peripheral sympathetic damage is a frequent cause of anisocoria, but of course it is not the only one. It is important to distinguish sympathetically and parasympathetically conditioned cases of pupillary inequality. It is equally important to distinguish pre- and postganglionic sympathetic damage, because preganglionic damage may be located in the spinal cord, while postganglionic damage may be located near the ganglion in the neck, intracranially, or intraorbitally.

2. Supranuclear inhibitory fibers reach the third-nerve nucleus from the diencephalon. Interruption of these fibers causes characteristically fast, abrupt, "tonohaptic" light reflexes. This pupillary reflex pattern occurs in many types of diencephalic conditions as well as in extrapyramidal syndromes; it is interesting to note that it is regularly associated with primary glaucoma, both wide and narrow angle (Fig. 11, *2*).[21-24]

3. Diencephalic hyperirritability causes large pupils and W- or V-shaped light reflexes. Reactions to light in such conditions begin with a normal contraction, but the pupils redilate prematurely (Fig. 11, *3*).[21,25]

4. Diffuse conditions involving both the diencephalon and the midbrain may lead to similar W- and V-shapes of the light reflex.

In contrast to the pupillary behavior described above (Paragraph 3), the pupils are small and the reactions slower than normal (Fig. 11, *4*).[21]

This brief, schematic survey covers only some of the pupillary syndromes which are found, under the experimental conditions standardly used in our laboratory, in cases with focal lesions at various sites. Modifications of the experimental conditions, of course, bring about different sets of responses which also vary characteristically, according to the site of a lesion. These variations provide us with additional facts and enlarge the number of our diagnostic tests.

Finally, it should not be forgotten that, in view of the wide extent of the pupillary pathways, negative pupillographic findings may be just as important as positive findings.

It was the basic idea upon which pupillography was founded by one of us (O. L.), about 30 years ago, that careful analysis of abnormal pupillary reflex shapes allowed definite clinical conclusions to be drawn as to the existence and location of lesions within the nervous network of pupillary control. The diagnostic system of pupillography was sometimes compared with that of perimetry. The analogies are evident. In the optic nerve, optic chiasm, and anterior part of the optic tract, the two methods cover structures of the same area. The differences between the two methods are just as evident. Field studies are concerned with parts of the telencephalon which are not reached by pupillary pathways. Pupillographic studies are concerned with parts of the brain stem not reached by visual pathways. The basic idea of localizing defects is the same.

It is hoped that the new instrument will make both the method and the diagnostic system of pupillography available to clinicians in ophthalmology, neurology, psychiatry, and internal medicine.

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Abnormal Accommodative Convergence in Squint

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Introduction

It is an imposing accomplishment of the visuomotor innervating system to continue deftly repositioning a pair of retinas so that single binocular vision is enjoyed while the eyes are scanning a distant scene. Yet, still more impressive is the ability to instantaneously shift the eyes from the distant scene to a wrist watch, identify the time, and immediately refixate the distant panorama. This feat of a swift, precise, coordinated change in the optics and alignment of the eyes which provides the finest detail of the near visual pattern to be sharply and singly seen is made possible by the near vision complex. The simultaneous application of many distinct phenomena during fixation at near makes up the near vision complex, the most important being (1) accommodation, (2) accommodative convergence, (3) fusional vergence, (4) fixation movement (version), and (5) pupillary constriction. This paper deals only with the first three components of the near vision complex, i. e. (1) accommodation, (2) accommodative convergence, and (3) fusional vergence.

Physiological Relationship of Accommodation and Accommodative Convergence.— In response to the stimulus to fixate at near, innervation is concomitantly dispatched in a proportionate manner to the ciliary muscles for accommodation (A) and the medial recti for accommodative convergence (AC). Perhaps an electronic investigative system could be developed that would facilitate scientific study of the pattern by which A and AC are innervationally associated, but clinically it is impractical to consider such a possibility. It is quite practical, however, to deduce what the nature of the innervational association of A and AC is by studying the findings of the prism and alternate-cover test performed at 6 meters and 0.33 meter. These measurements must be conducted while the examiner controls the patient's accommodation. This stipulation can be satisfied by (1) providing the patient with lenses that fully correct his ametropia and (2) requiring the identification of small symbols that are used as fixation targets rather than employing a muscle light.

Identifying small symbols at 6 meters through ametropic spectacle correction requires zero A, and naturally there is associated a zero amount of AC. At 0.33 meter fixation some A is needed to clear the vision and ideally there is associated the required amount of AC to permit bifoveal fixation of the small symbols. If this actually is the case, then A and AC issue forth in perfect harmony; the ratio of A to AC (A:AC) is perfect. A perfect A:AC is clinically recognized by the prism and alternate-cover measurements at 6 meters and 0.33 meter being identical.

That each person should possess a perfect A:AC is rightfully improbable. The A:AC may be imperfect in one of two ways; the A has associated with it either (1) an excessive or (2) a deficient AC. The first type of imperfect A:AC causes more esotropia ("eso") at 0.33 meter than at 6 meters in "eso"-aligned patients, whereas the latter causes less. In "exo"-aligned conditions excessive AC causes less exotropia ("exo") at near, while deficient AC causes greater.

All possible degrees of imperfection exist, regardless of which type of A:AC happens to be present. The fusional vergences, fortunately, can cope with the vast majority of small degrees of improper alignment produced by an imperfect A:AC. Consequently,

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small differences in the prism and alternate-cover measurements between distance and near fixation are nothing to be disturbed over. Some imperfect ratios however, cause a vast difference between 6 meter and 0.33 meter findings and cannot avoid being labeled as abnormal. Where to draw the arbitrary line that separates those that are obviously outside normal limits from the ones barely within remains a matter of conjecture. This is a natural difficulty, since the degree of "eso" or "exo" caused by an imperfect A:AC that can be compensated by the horizontal fusional vergence is variable from person to person. Even the same person's capacity to overcome the misalignment is subject to change with time or treatment.

Clinical Study

A study of the A:AC in 1249 children, ranging from 3 months through 12 years of age, with comitant esotropia or exotropia was carried out. In order to be accepted into the study the patient had to meet the following criteria:

1. There was comitance in all fields of gaze, secondary overaction of the inferior obliques excepted.

2. The horizontal strabismus could not be compounded by a vertical factor of more than 5△ as determined by prism and alternate-cover examination in the primary position.

3. Unilateral amblyopia could not be greater than 0.4.

4. Anisometropia could not be greater than 1.5 D. between the spherical equivalents.

5. The examination and treatment of each case was done by the same ophthalmologist (M. M. P.), orthoptics excepted.

Since this study deals with a series of cases, rather than individual patients, an arbitrary standard had to be adopted which defined normal and abnormal A:AC. Any difference between the 6 meter and 0.33 meter prism and alternate-cover measurements that was 10△ or less was considered normal A:AC; a difference of greater than 10△ was classified as abnormal.

The study was divided into three parts. The first illustrates the differences and similarities in onset age and ametropia between the strabismus groups having normal A:AC and those having abnormal A:AC. The second presents the results of attempts to alter the abnormal A:AC in strabismus. The third cites the results of attempts to increase the fusional divergence in esotropes having abnormal A:AC.

Part I. The Interrelationship Between the A:AC, the Age of Onset of the Strabismus, and the Ametropia in Comitant Horizontal Heterotropias

The three objectives were to determine (1) the incidence of abnormal A:AC in esotropia and exotropia, (2) the relationship between both normal and abnormal A:AC and age of onset of the strabismus, and (3) the relationship between both normal and abnormal A:AC and the ametropia of the strabismic patient.

Incidence of Abnormal A:AC Among Children with Comitant Horizontal Heterotropia.—Of the 1249 cases there were 897 esotropes and 352 exotropes (Table 1). 414 (45.8%) of the esotropes and 207 (58.8%) of the exotropes had an abnormal A:AC. All 414 esotropes with abnormal A:AC had greater "eso" at near than at distance fixation. Of the 207 exotropes having abnormal A:AC, 86.6% had the type which caused

TABLE 1.—*Percentage of Children with Comitant Horizontal Heterotropia Having Abnormal A:AC* *

	Total	Normal A:AC	Abnormal A:AC	Type of Abnormal A:AC	
Esotropes	897	483 (54.2)	414 (45.8)	414 (100)	Greater "eso" at N than D
				0 (0)	Less "eso" at N than D
Exotropes	352	145 (41.2)	207 (58.8)	179 (86.6)	Less "exo" at N than D
				28 (13.4)	Greater "exo" at N than D
Total	1249	628 (50.3)	621 (49.7)		

* Percentages are given in parentheses.

TABLE 2.—*Percentages of Children with "Congenital" and Acquired Comitant Horizontal Heterotropia* *

	"Congenital"	Acquired	Total
Esotropes	230 (25.6)	667 (74.4)	897
Exotropes	Impossible to classify adequately		352

* Percentages are given in parentheses.

TABLE 3.—*Percentages of Abnormal A:AC in Cases of "Congenital" and Acquired Esotropia* *

	Total Cases	Normal A:AC	Abnormal A:AC
"Congenital"	230	194 (84.3)	36 (15.7)
Acquired	667	289 (43.3)	378 (56.7)
Total	897	483	414

* Percentages are given in parentheses.

less "exo" for near than for distance, while 13.4% had the opposite type.

Relationship of Normal and Abnormal A:AC to Age of Onset of Comitant Esotropia.—An attempt was made to determine the age of onset of the strabismus in all instances. Difficult as this task was, it was possible to recognize two distinct groups among the esotropes. In one, the esotropia was present at birth or within the first several weeks after birth. This group was labelled "congenital," and 25.6% of 897 esotropes were of this category (Table 2). All who had "straight" eyes at birth but whose eyes first "crossed" after 6 months of age (74.4%) were classified as having acquired cases.

It became obvious that in exotropes, as a group, it was impossible to determine the age of onset accurately. Because of its fleeting nature, the parents all too often were guessing when they tried to list the age of onset.

There was a significant difference between the percentages of children with "congenital" and acquired esotropia having abnormal A:AC. It occurred in 15.7% of 230 cases of "congenital" esotropia but loomed to 56.7% among 667 cases of acquired esotropia (Table 3).

Regardless of whether the patient with acquired esotropia had a normal or an abnormal A:AC, the graphic distributions of the various ages of onset, as well as the average age of 2½ years at onset, were similar (Figs. 1 and 2).

Relationship of Normal and Abnormal A:AC to Ametropia in Comitant Esotropia.

The maximal cycloplegic refractive error on the patient's record was converted into spherical equivalents. The spherical equiv-

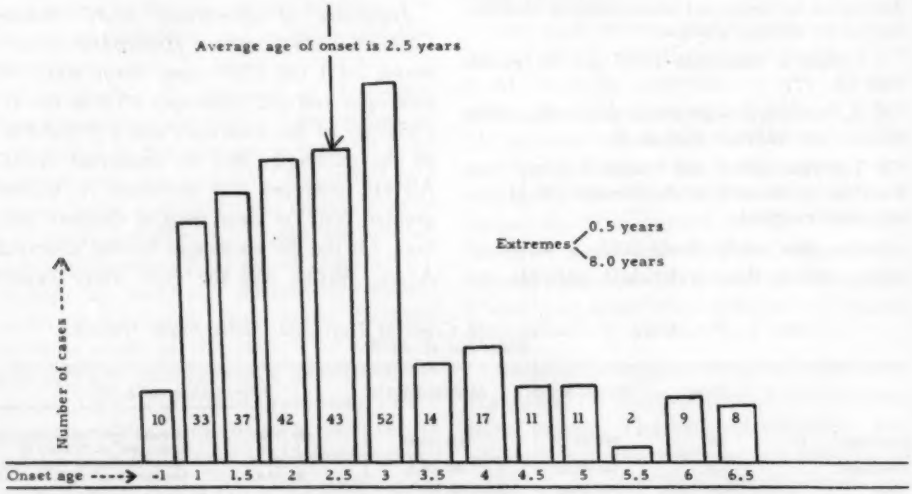

Fig. 1.—Age of onset among 289 patients with acquired comitant esotropia having normal A:AC.

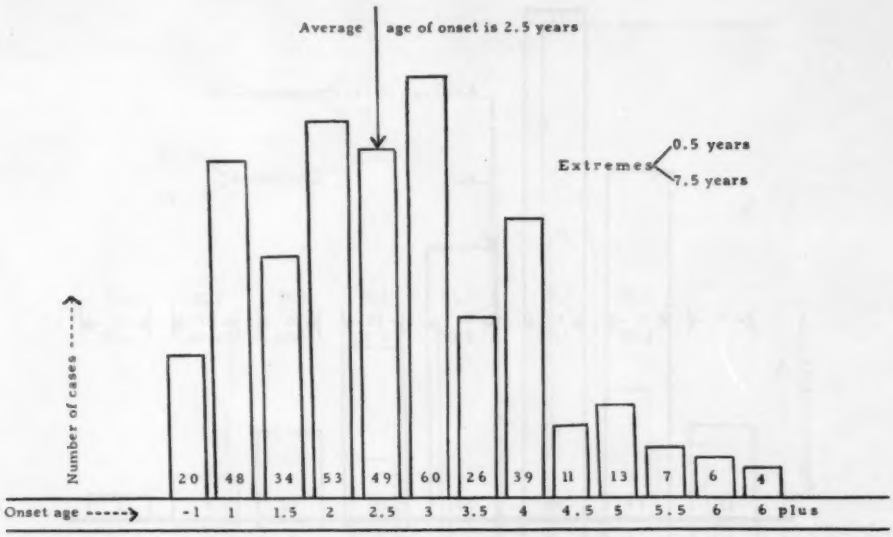
Average age of onset is 2.5 years
Extremes 0.5 years
7.5 years
Number of cases
20 48 34 53 49 60 26 39 11 13 7 6 4
Onset age
-1 1 1.5 2 2.5 3 3.5 4 4.5 5 5.5 6 6 plus

Fig. 2.—Age of onset among 370 patients with acquired comitant esotropia having abnormal A:AC.

alent in the least ametropic eye was recorded in 897 patients with esotropia.

The degrees of ametropia among "congenital" esotropes were similar despite the A:AC being normal or abnormal (Figs. 3 and 4). The average hypermetropia was 2.25 for those with normal A:AC and 2.00 for the group with abnormal A:AC.

Among the patients with acquired esotropia with normal A:AC there was a conspicuous increase in the number having large degrees of hypermetropia (Fig. 5). Their average hypermetropia was 4.75.

The patients with acquired esotropia with abnormal A:AC tended to have a quantity of hypermetropia similar to that found in patients with "congenital" esotropia. Figure 6 shows that their average hypermetropia was 2.25.

Comment.—This report brings into focus the fact that the type of abnormal A:AC having excessive AC associated with each diopter of A should be ranked with equal importance to hypermetropia as an etiological factor of acquired esotropia. Several facts bear this out. 1. The 2.25 average hypermetropia of patients with acquired esotropia with abnormal A:AC is not too unlike the average hypermetropia found in children free of strabismus. Therefore, some factor other than hypermetropia must provoke the onset of esotropia in this group. 2. Since 56.7% of patients with acquired esotropia had an abnormal A:AC, as contrasted to 15.7% of the "congenital" group, some cause-and-effect relationship between abnormal A:AC and acquired esotropia must exist. 3. Those having normal ratios and an average hypermetropia of 4.75 comprised slightly less than half the total patients with acquired esotropia, whereas the remainder were made up of those with abnormal A:AC and an average hypermetropia of 2:25. This suggests that hypermetropia alone accounts for no more acquired esotropia than a somewhat similar number caused by an abnormal A:AC.

Since either hypermetropia or abnormal A:AC causes esotropia upon the response of accommodation, a very large segment of the patients with acquired esotropia suffer a combination of these two isolated etiologic factors. In general, however, the hypermetropic factor alone must be large to incite

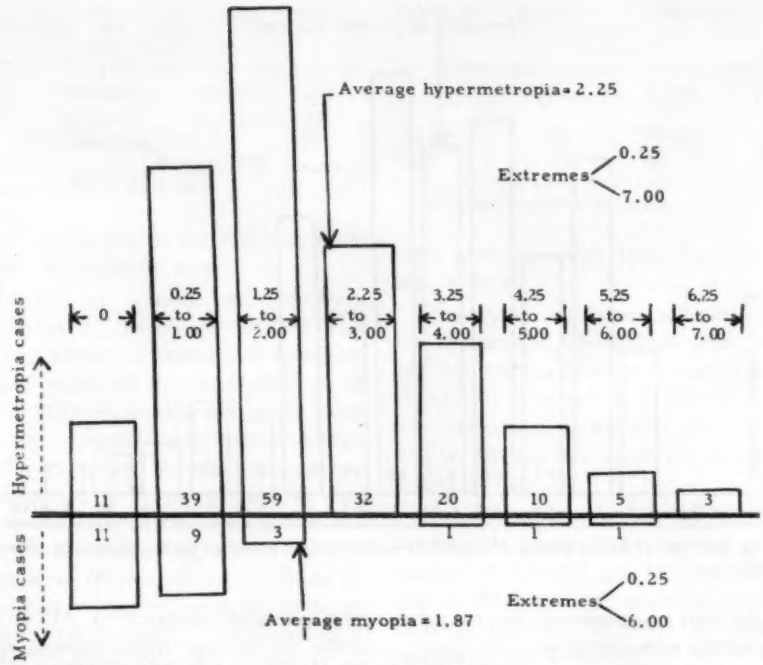

Fig. 3.—Ametropia found among 194 patients with "congenital" comitant esotropia having normal A:AC.

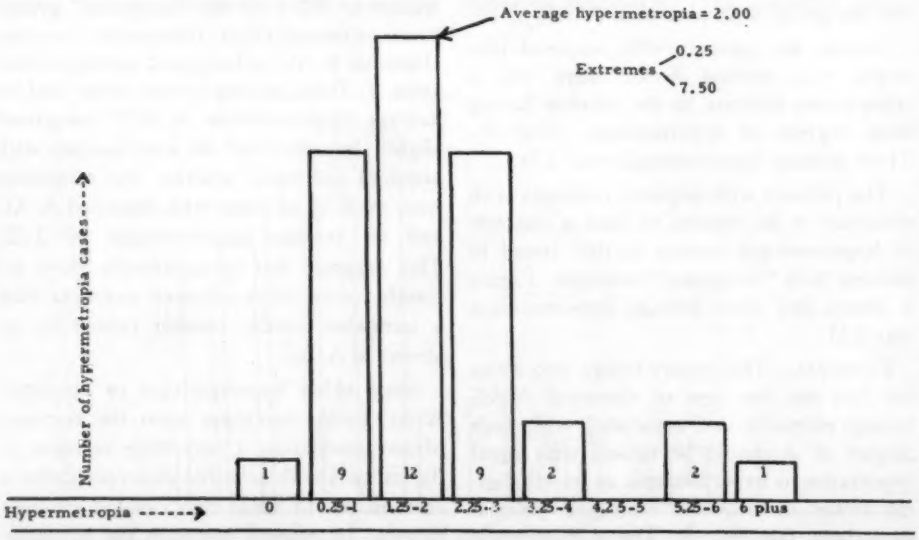

Fig. 4.—Ametropia found among 36 patients with "congenital" comitant esotropia having abnormal A:AC.

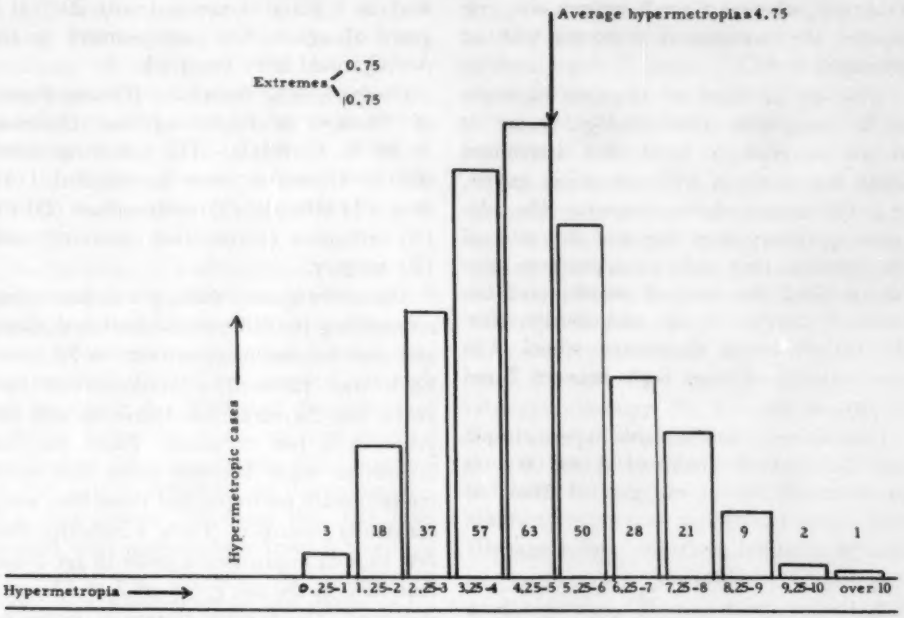

Fig. 5.—Ametropia found among 289 patients with acquired comitant esotropia having normal A:AC.

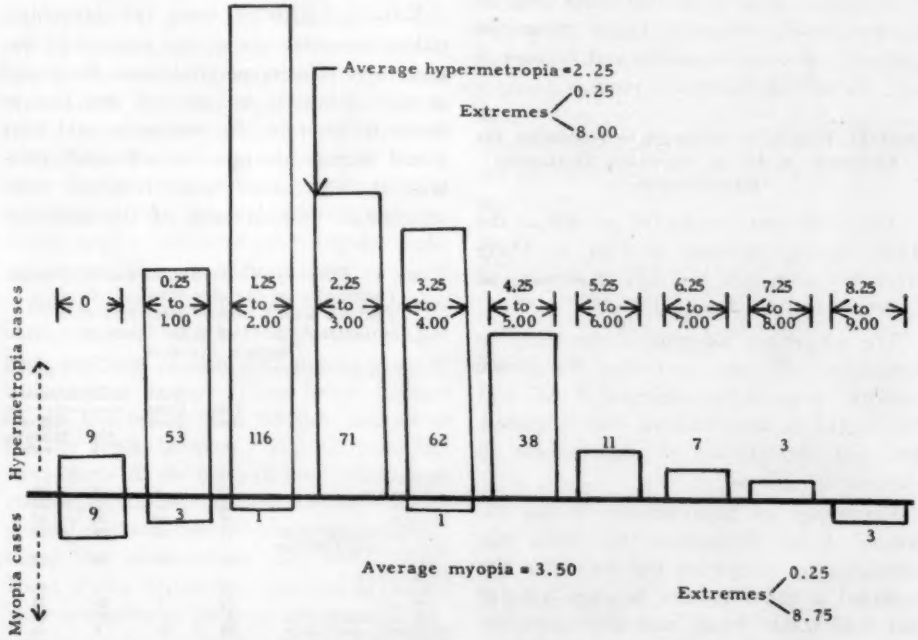

Fig. 6.—Ametropia found among 378 patients with acquired comitant esotropia having abnormal A:AC.

esotropia, whereas a small amount will precipitate the esotropia if it occurs with an abnormal A:AC.

The age of onset of acquired esotropia is the same with either etiologic factor. It is not the etiologic factor that determines when the esotropia will commence; rather, it is the accommodation response. The adequate accommodation response that sets off the esotropia may make its appearance anywhere along the span of development between 8 months of age and shortly after the patient enters elementary school. The vast majority of cases begin between 2 and 3 years of age.

Conclusions.—1. Excessive hypermetropia and the type of abnormal A:AC that is characterized by an exaggerated "eso" at near fixation constitute two separate etiologies of acquired esotropia; yet frequently they occur in combination.

2. Patients with acquired esotropia have an abnormal A:AC three times oftener than do those with "congenital" esotropia.

3. Acquired esotropias that result from an accommodative response begin when the patient is between 8 months and 7 years of age, the average being 2½ years.

Part II. Results of Attempts to Normalize the Abnormal A:AC in Comitant Horizontal Heterotropias

This study was conducted on 668 of the 1249 children reported in Part I. There were 494 esotropes and 174 exotropes, all of whom had an abnormal A:AC.

The objectives of this study were to determine (1) what particular therapeutic measures improve the abnormal A:AC, (2) the degree of improvement that is gained, and (3) the quality of improvement in various age groups.

Percentage of improvement in the abnormal A:AC throughout this paper was calculated by comparing the reduction that occurred in the difference between 6 meter and 0.33 meter prism and alternate-cover measurements. For instance, if the difference between 6 meters and 0.33 meter was 40△ at 4 years of age and only 20△ at 7 years of age a 50% improvement in the A:AC would have occurred.

Comparison of Results of Various Forms of Therapy in Improving the Abnormal A:AC in Esotropia.—The following methods of treatment were investigated: (1) time, (2) bifocals, (3) isoflurophate (DFP), (4) orthoptics (dissociation exercises), and (5) surgery.

Time: No specific therapy was directed at normalizing the differences between distance and near fixation measurements in 73 cases. Each was followed a minimum of two years, and the maximum follow-up was six years in a few instances. There was no distinction made between those that were intermittently esotropic and those that were constantly esotropic. Table 4 indicates that few showed improvement prior to age 5 but that 50% in the age group of 7 to 12 years improved. The average degree of improvement in the abnormal A:AC among those that did improve was 65%.

Bifocals: Bifocals were not prescribed unless binocular vision was present at distance and convergent strabismus developed at near fixation. An attempt was always made to provide the minimum add that would permit identification of small symbols at 0.33 meter with freedom from strabismus. Improvement of the abnormal

TABLE 4.—*Effect of No Treatment and of Various Treatments on the Abnormal A:AC in Patients with Comitant Esotropia with Greater "Eso" at Near Than at Distance Fixation*

	Total Cases	A:AC Unimproved	A:AC Improved	
			No.	% of Improvement
No treatment				
Below 5 yr.	11	9	2	40
5–7 yr.	22	15	7	69
7–12 yr.	40	20	20	67
All ages through 12 yr.	73	44	29	65
Bifocals, all ages through 12 yr.	151	132	19	52
Isoflurophate				
Below 5 yr.	15	11	4	81
7–12 yr.	32	4	28	62
All ages through 12 yr.	47	15	32	64
Orthoptics, ages 7–12 yr.	39	35	4	53
Surgery, all ages through 12 yr.	184	41	143	73

A:AC was experienced by 19 children among 151 who had worn bifocals for a minimum of two years. The average improvement of the difference between distance and near measurements among these 19 that did improve was 52% (Table 4). None of the 151 children that were studied had been treated with isoflurophate, orthoptics, or surgery.

Isoflurophate: Isoflurophate almost always caused the difference between the 6 meter and 0.33 meter prism and alternate-cover measurements to vanish when a concentration of 0.025% was instilled into each eye once each day. However, the important time to judge the merits of isoflurophate medication in normalizing the abnormal A:AC ratio is following its discontinuance. For that answer, 47 cases that had been treated with isoflurophate from 6 weeks to 18 months were studied. The investigation took place a minimum of six weeks and a maximum of one year following the discontinuance of isoflurophate. The isoflurophate was first prescribed as a 0.025% concentration and 1 drop was instilled in each eye each morning. In successive weeks or months the concentration was reduced first to 0.0125% and later to 0.00625%. Eventually the frequency of instillation of 0.00625% strength was reduced to every other day as the medication was gradually withdrawn. This general scheme was referred to as a routine of gradually diminishing concentration of isoflurophate.

All 47 children studied had enjoyed binocular vision at distance with glasses but were esotropic at near with glasses prior to isoflurophate therapy. Those below 5 years of age had never worn bifocals, and all in the age group between 7 and 12 years had worn them. At the onset of the isoflurophate routine, all had their glasses removed and remained without them during the entire interval that isoflurophate was administered. None of the 47 had been previously treated with orthoptics or surgery.

Lasting improvement of the abnormal A:AC occurred in 4 of 15 children in the age group below 5 years, whereas 28 of 32 had durable improvement in the group of children aged 7 years and over. In the whole group, there was a 64% improvement among the 32 children whose ratio was improved (Table 4).

Orthoptics: In 39 patients treated with dissociation exercises a comparison was made of the A:AC determined prior to therapy and that measured six weeks to one year after orthoptics was discontinued. All 39 patients had binocular vision at distance with glasses but were "crossed" at near through the upper segments and "straight" through the lower segments of their bifocals. They were all 7 years or older prior to being treated with exercises. None had been treated previously with isoflurophate or surgery.

Table 4 shows that only four derived any lasting improvement in their abnormal A:AC. Despite the fact that many could for the first time maintain "straight" eyes and clear vision at both distance and near unaided by glasses after their program of orthoptics, the exaggerated "eso" at near, as elicited by alternate-cover test, was relatively unchanged over what it was prior to treatment. They had been converted from esotropia to esophoria with no real change in the abnormal pattern of associated innervation of A and AC.

TABLE 5.—*Percentage of Improvement in the Abnormal A:AC by 205 Operations Performed on 184 Patients with Comitant Esotropia Having Greater "Eso" at Near Than at Distance Fixation*

	Operations	% of Improvement in A:AC by 1st Operation	% of Improvement in A:AC by 2d Operation	Total Av. % of Improvement A:AC by Surgery
Recession MROU	104	66	--	66
Followed by resection LROU	6	27	28	55
Recession of only one MR	74	38	--	38
Followed by recession of 2d MR	15	24	33	57
Resection LROU	4	21	--	21
Resection of only one LR	1	0	--	0
Recession MR, resection LR	1	100	--	100
Total operations	205	54	32	51

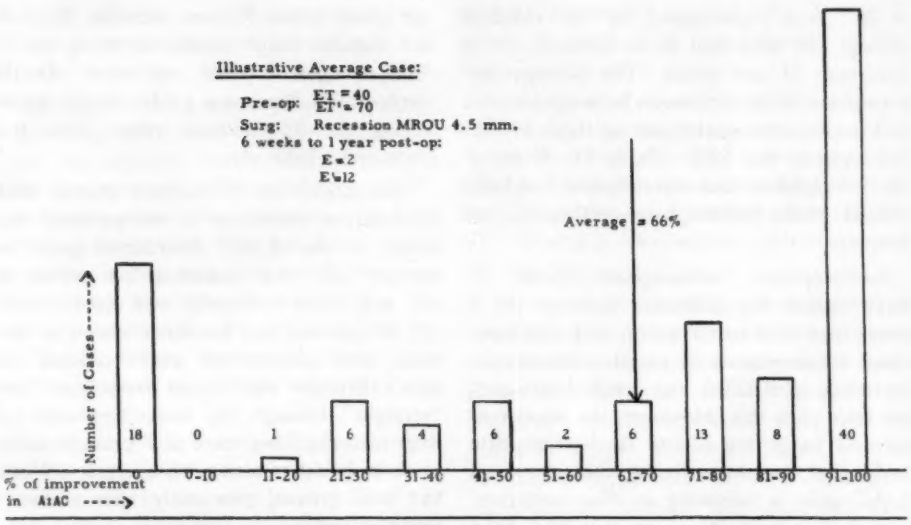

Fig. 7.—Results of medial rectus recessions, O. U., on the abnormal A:AC in 104 patients with comitant esotropia having greater "eso" at near than at distance fixation.

Surgery: Surgery, as is statistically borne out by Table 4, improved the abnormal A:AC in 143 patients with constant esotropia among 184 that were operated on. Among those improved, the average abnormal A:AC was 73% more normal six weeks to one year after operation. However, of all 205 operations performed on the 184 patients, the average improvement in the abnormal A:AC per operation was only 51% (Table 5).

The recession of the medial recti was consistently the most successful surgical technique, and it was performed in 104 cases, with resulting 66% improvement in the abnormal A:AC (Fig. 7). There were 40 cases that had near-complete normalization of the abnormal A:AC, while 18 had no improvement. Recession of only one medial rectus was not as successful as recessing both (Fig. 8). Among 74 patients who had only one medial rectus recessed the improvement in the abnormal A:AC was only 38%.

Table 6 summarizes the results of various forms of therapy upon the abnormal A:AC in esotropes.

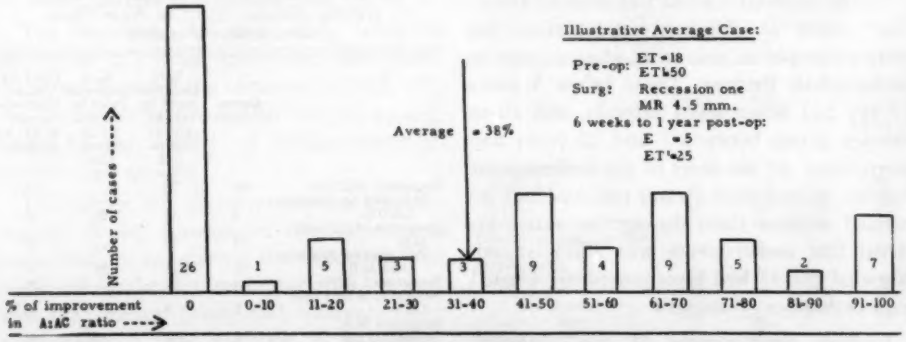

Fig. 8.—Results of recession of one medial rectus on the abnormal A:AC in 74 patients with esotropia having greater "eso" at near than at distance fixation.

TABLE 6.—*Effects of Various Forms of Therapy upon the Abnormal A:AC in 494 Patients with Comitant Esotropia Having Greater "Eso" at Near Than at Distance Fixation* *

Treatment	Total Cases	A:AC Unimproved	A:AC Improved	
			No.	% of Improvement
Nothing	73	44 (60)	29 (40)	65
Bifocals	151	132 (88)	19 (12)	52
Isoflurophate	47	15 (37)	32 (68)	64
Orthoptics	39	35 (90)	4 (10)	53
Surgery	184	41 (22)	143 (78)	73
All forms of therapy	494	267 (54)	227 (46)	69

* Percentages are given in parentheses.

TABLE 7.—*Effect of No Treatment, of Orthoptics, and of Surgery on Abnormal A:AC in Patients with Comitant Exotropia Having Less "Exo" for Near Than for Distance Fixation*

	Total Cases	A:AC Unimproved	A:AC Improved	
			No.	% of Improvement
No treatment				
Below 5 yr.	4	3	1	25
5–7 yr.	3	1	2	75
7–12 yr.	15	9	6	58
All ages to 12 yr.	22	13	9	56
Orthoptics, 6–12 yr.	16	16	0	--
Surgery, all ages to 12 yr.	124	13	111	68

Comparison of Results of Various Forms of Therapy in Improving the Abnormal A:AC in Exotropia.—Table 1 shows that 179 of 207 exotropes having abnormal A:AC had less "exo" at near than at distance. The remaining 28 had greater "exo" at near than distance. This study of therapy deals with 162 of the 179 exotropes that had less "exo" at 0.33 meter than at 6 meters and 12 of the 28 with the opposite type of abnormal A:AC. The following methods of treatment were investigated: (1) time, (2) orthoptics, (3) surgery.

Exotropes with Less "Exo" at Near Than at Distance Fixation: Time. Twenty-two exotropes with less "exo" at near than at distance were followed from two to six years, during which time they received no therapy for their abnormal A:AC. Table 7 demonstrates that the abnormal A:AC improved in nine and that their average improvement was 56%.

Orthoptics. Table 7 illustrates that 16 exotropes with abnormal A:AC had comparable 6 meter and 0.33 meter prism and alternate-cover measurements before orthoptics and six weeks to one year after orthoptics.

Surgery. Surgery improved the abnormal A:AC (Table 7) of 111 of 124 exotropes. Among the 111 that were improved the abnormal A:AC averaged 68% better six weeks to one year after surgery.

These 124 patients had 126 operations (Table 8), 121 being recessions of the lateral recti, 2 of which were followed by resection of the medial rectus or recti. One lateral rectus only was recessed in three operations, and this procedure yielded no change in the abnormal A:AC. The average improvement for all 126 operations on the 124 patients was 67% reduction in the difference between distance and near measurements.

TABLE 8.—*Percentage of Improvement in the Abnormal A:AC by 126 Operations Performed on 124 Patients with Comitant Exotropia Having Near Fixation Measurements Less Than Those of Distance Fixation*

	Operations	% of Improvement in A:AC by 1st Operation	% of Improvement in A:AC by 2d Operation	Total Av. % of Improvement in A:AC by Surgery
Recession LROU	121	69	--	69
Followed by resection of one MR	1	50	25	75
Followed by resection of MROU	1	10	90	100
Recession of only one LR	3	0	--	0
Total operations	126	67	58	67

The 121 patients (Fig. 9) that were first operated on by recession of their lateral recti had the following final results: 48 experienced improvement of their abnormal A:AC by 91% to 100%; 10 had no improvement; the remaining 63 obtained partial improvement that was rather evenly spread from 0 to 90%. The average improvement in the abnormal A:AC was 69%.

Table 9 summarizes the effects of various forms of therapy in exotropes having less "exo" at near than at distance fixation.

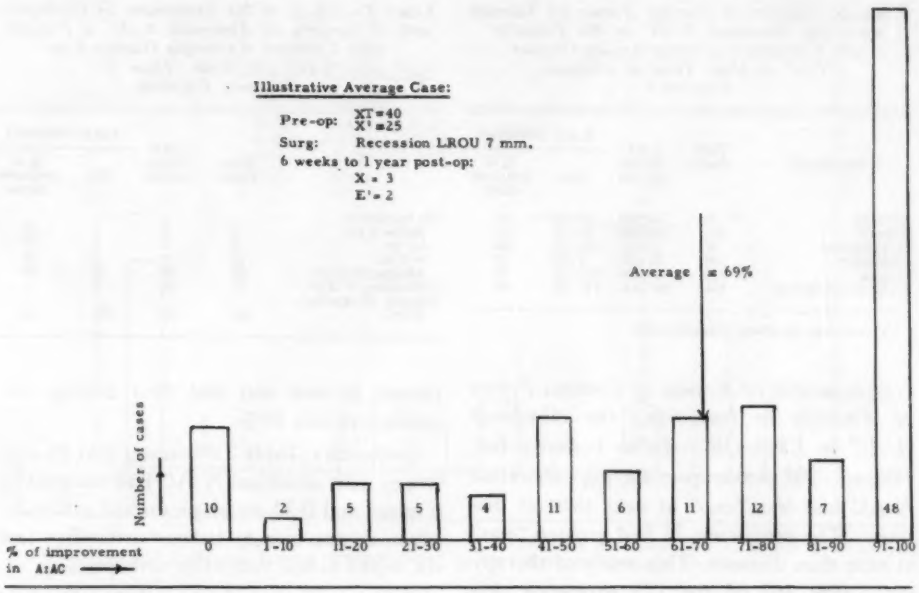

Fig. 9.—Results of lateral rectus recessions, O. U., on the abnormal A:AC in 121 patients with comitant exotropia having less "exo" at near than at distance fixation.

Exotropes with Greater "Exo" at Near Than at Distance Fixation: Exotropic children having this type of abnormal A:AC are not nearly as numerous as those possessing the opposite type. The number of patients in this category who were followed and who received no specific therapy or orthoptics for their abnormal A:AC was insufficient to justify presentation of results. However, Figure 10 depicts the improvement in the abnormal A:AC in 12 such cases surgically treated with lateral recti recessions. The average reduction in greater "exo" at near than at distance was 81%.

TABLE 9.—*Effect of Various Forms of Therapy Upon the Abnormal A:AC in 162 Patients with Comitant Exotropia Having Less "Exo" for Near Than for Distance Fixation* *

	Total Cases	A:AC Unimproved	A:AC Improved	
			No.	% of Improvement
No therapy	22	13 (59)	9 (41)	56
Orthoptics	16	16 (100)	0 (0)	0
Surgery	124	13 (10)	111 (90)	68
All forms of therapy	162	42 (26)	120 (74)	67

* Percentages are given in parentheses.

Comparison of the Results of Various Forms of Therapy upon the Abnormal A:AC in Esotropes and Exotropes Having Near Fixation Measurements That Are More Convergent Than Those of Distance Fixation.—Regardless of whether the strabismus be an esotropia or an exotropia, the per cent of improvement in the abnormal A:AC is comparable for different types of therapy (Table 10). With no therapy, about 40% improved with time. Orthoptics does not significantly alter the abnormal ratio, while surgery performed on either esotropes or exotropes does well in more than three-fourths of all cases operated on.

Comment.—Esotropia: Time alone, during which no specific therapy is directed at the abnormal A:AC, is frequently associated with a gradual spontaneous improvement of the A:AC in children over 7 years of age. Although the over-all prognosis is more often than not a happy one, still this is not too helpful when one is first confronted with the clinical problem that characteristically has at its inception crossed eyes at near with straight eyes at distance fixation, either

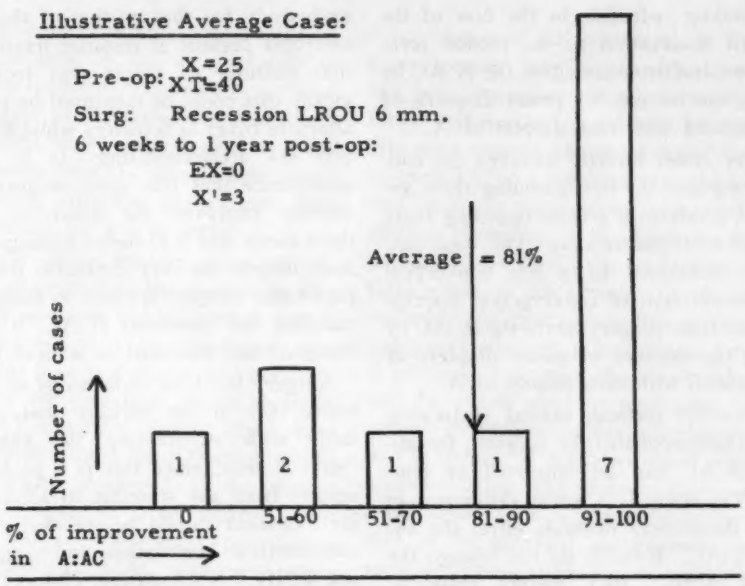

Fig. 10.—Results of lateral rectus recessions, O. U., on the abnormal A:AC in 12 patients with comitant exotropia having greater "exo" for near than for distance fixation.

with or without glasses. This is all the more apparent when it is realized that this is a problem prevalent in the 4-year-old and under age bracket. The visual symptoms of diplopia and visual confusion, the sorry appearance of esotropia occurring at near fixation, and the possibility of a constant esotropia being triggered off collectively constitute adequate cause for instituting treatment specifically designed to control this problem.

TABLE 10.—*Comparison of Effectiveness of Various Forms of Therapy upon the Abnormal A:AC in 296 Esotropes and 162 Exotropes Having Near Fixation Measurements That Are More Convergent Than Those of Distance Fixation* *

	Total Cases	A:AC Unimproved	A:AC Improved	
			No.	% of Improvement
No therapy				
Esotropia	73	44 (60)	29 (40)	65
Exotropia	22	13 (59)	9 (41)	56
Orthoptics				
Esotropia	39	35 (90)	4 (10)	53
Exotropia	16	16 (100)	0 (0)	0
Surgery				
Esotropia	184	41 (22)	143 (78)	73
Exotropia	124	13 (10)	111 (90)	68

* Percentages are given in parentheses.

Bifocals do poorly at improving the abnormal A:AC, but they are important therapeutically, since they so adequately compensate for it. The lower bifocal segment reduces the need for accommodation at near, and this allows the tendency to convergent strabismus caused by the abnormal association of A and AC to be hidden. However, despite bifocals holding the effects caused by the abnormal A:AC in check, the abnormal ratio is not likely to be changed more than what one would expect from time alone, with no therapy.

Both isoflurophate and surgery tend to normalize the abnormal A:AC. Isoflurophate alters the A:AC by conditioning the myoneural junction of the ciliary muscle so that innervation dispatched to the ciliary muscles causes an exaggerated accommodation response. This results in a reduction of the amount of accommodation innervation required to produce a certain dioptric increase in the lenticular refraction. Associated with this lessening of innervation flowing to the ciliary muscles, while the quantity of A remains unchanged, is a

corresponding reduction in the flow of the associated innervation to the medial recti. Therefore, isoflurophate alters the A:AC by reducing the number of prism diopters of AC associated with each diopter of A.

Surgery either directly weakens the converging muscles or, by tightening their antagonists, produces a greater opposing force to medial recti contraction. The final outcome is attainment of a less convergent alignment per unit of convergence innervation. Therefore, surgery alters the A:AC by reducing the number of prism diopters of AC associated with each diopter of A.

By whatever method, optical (bifocals), medical (isoflurophate), or surgical, the abnormal A:AC can be improved or controlled. Yet there is a great difference in the way these three methods effect the abnormal A:AC. Bifocals do not change the abnormal A:AC; they merely mask it. Isoflurophate causes a short-lived but ever-changing (dynamic) effect upon the abnormal A:AC. Surgery imposes a permanent and constant (static) improvement upon the abnormal A:AC.

Isoflurophate apparently does exert some degree of permanent improvement on the abnormal A:AC. The exaggerated "eso" that was present at near, prior to treatment, may not fully return, even though many months will have passed since the isoflurophate was discontinued. This effect of isoflurophate is not easily explained. Perhaps the hypertrophied medial recti revert back to more normal muscles after isoflurophate forces them into relative inactivity for a few months, and, following discontinuance of the isoflurophate, the former hypertrophy never fully returns. At any rate, in this respect the lasting improvement of the abnormal A:AC produced by isoflurophate is similar to the permanent result attained by surgery.

This study could possibly lead one to deduce that surgery is indicated in the treatment of abnormal A:AC in esotropia. This is unfortunate and unintended, since the surgery reported in this paper was performed exclusively for that portion of the constant esotropia present at distance fixation. Only that quantity of tropia was treated surgically that could be measured by prism and alternate cover at 6 meters while the patient was not accommodating. It is a happy coincidence that this same surgery so frequently improved the difference between the 6 meter and 0.33 meter findings. Therefore, despite the very creditable showing on paper that surgery appears to make in normalizing the abnormal A:AC, it was not designed and executed to achieve this end.

Surgery has little claim to be assigned an active role in the therapy that primarily deals with suppressing the exaggerated "eso" at near, since this is a problem that results from the stimulus to accommodate. Its treatment should be one that curbs accommodation innervation, and surgery does not satisfy this stipulation. Unless there is a sizable esophoria or tropia at 6 meters preoperatively while the patient is not accommodating, one can expect an exotropia postoperatively while the patient is not accommodating.

Exotropia: Among children with intermittent exotropia, the majority have an abnormal A:AC that makes for less "exo" at near than at distance fixation. A minority have the reverse type of abnormal A:AC, that is characterized by greater "exo" at near than at distance fixation. However, it has been shown that with aging alone, during which no therapy is carried out, the abnormal A:AC commonly tends toward improvement as revealed by the near "exo" measurement approaching the distance fixation measurement.

The salient question is this: "Why does an abnormal A:AC that causes greater than normal convergence for each diopter of accommodation tend to be existent in the majority of exotropic children?" It is not the cause of the exotropia. But its presence could certainly be an adaptation to gain the greatest amount of convergence possible by accommodating to overcome the normal infantile hypermetropia and thereby assist the

fusional convergence in acquiring parallelism of the visual axes. A similar adaptation of the A:AC is frequently observed in a myope who has never worn glasses for near work. Upon his first wearing spectacle correction for near work there is considerable "eso," which vanishes after the glasses have been worn constantly for a few weeks.

This study offers another piece of evidence that adaptation is the answer to why the majority of young intermittent exotropes develop the type of A:AC that causes less "exo" at near than at distance. Theoretically, any surgery for exotropia should magnify this type of abnormal A:AC, since converging muscles must be tightened or diverging muscles weakened if the distant "exo" measurement is to be improved. But the happy surprise this study provides is that the abnormal A:AC improves rather than worsens with surgery. Such an ending is suggestive that the compensatory abnormal A:AC finds itself no longer useful postoperatively and consequently adjusts itself toward normal. Hence, as weeks pass following surgical correction of intermittent exotropia the distance and near measurements tend to equal one another.

Orthoptics does not tend to alter the difference between distance and near measurements in intermittent exotropia, but, then, it should not be expected to do so if the abnormal A:AC is an adaptive phenomenon devised to help the same problem orthoptics is attempting to aid.

The fact that the type of abnormal A:AC which is manifested by less "exo" at near than at distance tends to normalize with age alone, and no treatment, indicates that the general trend in growing patients with intermittent exotropia is toward gradual surrendering of the compensatory abnormal ratio. Does this further mean that with increasing age intermittent esotropia, in general, tends to deteriorate toward becoming constantly exotropic? This study does not answer that question, but I am suspicious from clinical observation that such is the case.

In esotropia the abnormal A:AC that causes greater "eso" at near than at distance has been considered a primary etiological factor that wrecks binocularity. In exotropia, this same type of abnormal A:AC has been suggested to be a compensatory phenomenon that assists in maintaining threatened binocularity. Moreover, it has been implied that the abnormal A:AC in esotropia is very rigid while in intermittent exotropia it is malleable. At first glance this probably appears contradictory, but on closer inspection it is suggestive that the abnormal A:AC may be either rigid or malleable, with all various gradations of flexibility between the two extremes. If the association pattern of accommodation and accommodative-convergence innervation is abnormal in the direction of exaggerated convergence response upon accommodating, and is rigid, the clinical problem is apt to be an esotropia, assuming that all other factors are normal. In uncorrected myopia and disturbances of anatomical and tonus factors that cause divergent alignment of the visual axes, a malleable pattern of accommodation associated with hyperconvergence may develop that aids in holding the visual axes parallel. In the former example the A:AC is an etiological factor, and in the latter it is a compensatory factor.

Conclusions.—1. After the age of 7 many patients with esotropia that is more convergent at near than at distance and patients with exotropia that is less divergent at near than at distance spontaneously experience a lessening in the difference between distant and near measurements. This is attributed to the shifting toward normal of the abnormal A:AC.

2. Despite bifocals being valuable in controlling the exaggerated "eso" at near, actually the abnormal A:AC is not improved, since the bifocals merely compensate for it.

3. Isoflurophate also masks the exaggerated "eso" at near, but in children below the age of 7 this result is not lasting when the isoflurophate is discontinued. In the

age group over 7 years, a brief routine of diminishing strength isoflurophate has a good chance of inducing permanent improvement in the abnormal A:AC. To this end, isoflurophate makes an outstanding contribution.

4. Orthoptics (dissociation exercises) do not appreciably alter the abnormal A:AC which causes more convergent alignment of the visual axes at near than at distance fixation.

5. Although surgery remarkably improves the abnormal A:AC in both esotropia and exotropia, it is not therapy that can be recommended specifically for eliminating the difference between distance and near measurements. Surgery is therapy that is justified by, and executed for the purpose of correcting, the misalignment existent at distant fixation while the patient is not accommodating. Solely the presence of an abnormal A:AC does not justify surgery.

Part III. Results of Attempts to Increase the Fusional Divergence Amplitude in Patients with Comitant Esotropia Having Abnormal A:AC

This study was made on 71 esotropes whose abnormal A:AC was manifested by an exaggerated "eso" at near fixation. The objective was to determine if either (1) an orthoptic program of dissociation exercises or (2) a routine of diminishing isoflurophate concentration increased the fusional divergence amplitude. These sought-after answers were considered vital to the matter of therapy, since improvement conceivably could be forthcoming either by the A:AC changing toward normal or by the fusional divergence amplitude increasing to counter the hyperconvergence. Part II dealt with the subject of the A:AC changing toward normal; Part III will be confined to the matter of increasing the fusional divergence amplitude.

The entire group of patients were between 7 and 12 years of age, and all enjoyed single binocular vision while fixating at distance, although most of them required glasses. Many required bifocals in order to maintain binocular vision at near, and some had worn them for several years. None had been operated on, and no case had first been treated with orthoptics and then treated with isoflurophate, or vice versa.

Measurement of the fusional divergence amplitude was performed according to the following steps: 1. While the patient was reading small letters at 0.33 meter through glasses that fully corrected his ametropia, a prism and alternate-cover measurement was obtained. 2. While the reading at 0.33 meter was continued, the maximal minus or the least additional plus lens power was found that would permit binocular clear vision. 3. Through this additional lens power, determined in the previous step, and while the patient was still reading the small letters at 0.33 meter, a second prism and alternate-cover measurement was done. The difference between the prism and alternate-cover measurements determined in Steps 1 and 3 was considered to be the amplitude of fusional divergence.

The following criteria were employed to indicate improvement in the fusional divergence amplitude. The post-treatment amplitude had to be increased by 10△ or more over the pretreatment measurement, and the improvement had to persist a minimum of six weeks after discontinuance of treatment.

Technique of Therapy.—The dissociation exercises were conducted by orthoptists employing the generally accepted methods. It was the orthoptist's judgment that determined the length of time over which the orthoptic treatment extended, but in general this interval was between six weeks and six months..

The isoflurophate therapy was carried out exclusively by an ophthalmologist, and the treatment interval was four weeks to six months. The program of diminishing isoflurophate concentration used in this study was exactly similar to the routine described in Part II. Before a change was made in the concentration or frequency of instilla-

tion, the patient was evaluated to determine if binocularity was still present while he was reading fine print without glasses. No patient was treated who had more than +4.00 spherical equivalent of hypermetropia, 1.50 D. of astigmatism, or greater than 1.50 D. anisometropia.

Results of Therapy.—Thirty-nine children were treated with dissociation exercises (Table 11), and improvement of the fusional divergence amplitude persisted in twenty-five.

Table 11 also indicates that 32 patients received a routine of diminishing isoflurophate concentration and that the improved fusional divergence amplitude was lasting in 16.

Comment.—Both orthoptics and isoflurophate are capable of improving the fusional divergence amplitude, but each renders its favorable effect by a different approach. The effect of isoflurophate upon the A:AC is ever-changing, or dynamic, and this is the factor that permits the medication to expand the fusional divergence amplitude. As the isoflurophate effect wears off, an increasing amount of accommodation innervation is necessary to assure a sharp image, which is associated with a like increase in the accommodative convergence innervation. The alert child, with good binocular visual ability, will subconsciously apply progressively more fusional divergence to counter the increasing "eso" in an attempt to maintain fusion. This cycle, repeated day after day, insidiously increases the fusional divergence amplitude. Gradually, over a period of weeks, reducing the isoflurophate concentration and/or the frequency of instillation allows a partial return of the pretreatment A:AC. The gradual recurrence of this exaggerated "eso" during accommodation increases the task of the fusional divergence. If the fusional divergence amplitude successfully rises to meet the challenge, it is exercised and improved as long as fusion is maintained. Ultimately, by way of this routine, the fusional divergence amplitude may be enlarged to the degree that unaided it may encompass an "eso" and make it latent in the form of a phoria, whereas before treatment the same "eso" would have been a manifest tropia.

TABLE 11.—*Effect of Isoflurophate and Orthoptics Upon the Fusional Divergence Amplitude in Seventy-One Patients with Comitant Esotropia Having Greater "Eso" at Near Than at Distance Fixation* *

	Total Cases	Fusional Divergence Amplitude	
		Unimproved	Improved
Orthoptics	39	14 (36)	25 (64)
Isoflurophate	32	16 (50)	16 (50)

* Percentages are given in parentheses.

Dissociation exercises offer a frontal assault upon the fusional divergence, with the objective being to increase its amplitude. It requires a large amount of organization, labor, attention, and motivation on the part of the patient, his parents, and the orthoptist to achieve success. It is a much more painstaking type of therapy than isoflurophate.

By virtue of the vast differences in the nature of the two approaches to the same problem, undoubtedly some children are better suited to one than to the other form of therapy, and in some instances it may be advisable to use the two approaches simultaneously.

Conclusions.—1. Dissociation exercises accomplish a lasting improvement of the fusional divergence amplitude in more than one-half of the treated esotropic children having an abnormal A:AC.

2. A program of gradually diminishing isoflurophate concentration achieves the same result in about one-half of those treated.

Summary

Prism and alternate-cover measurements done under controlled accommodation circumstances at 6 meters and 0.33 meter on 1249 comitant esotropic and exotropic children revealed about one-half of each group to have more than 10△ difference between distance and near fixation. An abnormal ratio of accommodation and accommodative convergence innervation (A:AC) is blamed for this difference.

An abnormal A:AC that causes an exaggerated esotropia ("eso") at near is found four times oftener in acquired than in congenital esotropia. This type of abnormal A:AC is considered to be an etiological factor in acquired esotropia that ranks equal in importance to hypermetropia. It causes the exotropia ("exo") to be less at near in exotropes, and in this condition it is considered to be a secondarily developed compensatory factor intended to assist in the maintenance of single binocular vision.

Spontaneous improvement in the abnormal A:AC can be expected in about one-half of the strabismus cases after the age of 7.

Regardless of the age, bifocals control the symptoms produced by the abnormal A:AC in esotropia, but neither bifocals nor dissociation exercises appreciably improve the abnormal A:AC.

Isoflurophate (DFP) almost always normalizes the A:AC while it is used, but in young children with esotropia the abnormal ratio returns to approximately the pretreatment level when therapy is discontinued. By way of contrast, the A:AC tends to remain more normal in children 7 years of age and over after use of isoflurophate is stopped.

Surgery permanently improves the abnormal A:AC in the majority of both esotropes and exotropes; however, it is not justifiable therapy unless the distance fixation prism and alternate-cover measurement is sizable.

Fusional divergence compensates for the exaggerated "eso" provoked by the abnormal A:AC. Its amplitude may be increased in children 7 years of age and over by a brief program of dissociation exercises or diminishing isoflurophate concentration.

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The Management of Endophthalmitis Following Cataract Extraction

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Intraocular infection is perhaps the most dreaded of all the complications which may follow cataract extraction. When endophthalmitis is associated with a vitreous abscess, the chances of a successful end-result becomes very poor indeed. The introduction of modern chemotherapeutic and antibiotic agents has somewhat improved the outlook in these conditions in recent years, but intraocular infection has not yet become a complication to be viewed with equanimity.

Clinical and Experimental Observations

Between 1944 and 1948 occasional reports were published of the successful management of endophthalmitis by the sulfonamides and penicillin.[1-4] The successes, however, were few, and the outlook was not hopeful. The sulfonamides apparently penetrate the blood-aqueous barrier satisfactorily, but their narrow antibacterial spectrum limits their field of usefulness.

In 1944, von Sallmann and Meyer[5] demonstrated that penicillin, even when given systemically in massive doses, does not penetrate sufficiently into the vitreous to produce concentrations adequate to control intravitreal infections. Leopold,[6] in the following year, confirmed their observations, and in 1946 he and Nichols[7] showed that streptomycin is of limited usefulness in intraocular infections for the same reason.

With the introduction of the newer antibiotics, the situation gradually began to look somewhat more hopeful. Chlortetracycline (Aureomycin) and oxytetracycline (Terramycin), like the earlier agents, penetrated poorly into the intraocular fluids. Chloramphenicol (Chloromycetin), however, was not open to this objection. Experimental studies on rabbits by Leopold and his associates[8] in 1950 indicated that with it suitable concentrations could be achieved in the intraocular tissues and fluids for the control of most infections caused by bacteria sensitive to it. The high concentrations which they found by paracentesis in the secondary aqueous humor suggested to them that the permeability of the blood-aqueous barrier is so increased in the presence of inflammation that concentration of chloramphenicol adequate to combat infection can then penetrate the ocular fluids.

One conclusion which Leopold and his group derived from their study was that the systemic administration of chloramphenicol might be so effective that the necessity for intravitreal injections would be reduced. On the basis of these experimental studies, as well as their subsequent clinical experience, these authors recommended large doses of chloramphenicol (3 gm. orally as the initial dose and 0.5 gm. every four hours thereafter) to combat intraocular infections.

Clinical results bore out these experimental observations. In 1951, Leopold[9] reported the use of chloramphenicol in six cases in which infection had developed after operation or had been introduced by foreign bodies. In three cases there was no response at all, though the failure might have been expected, since the bacteria present were not sensitive to this agent; there had also been no response to streptomycin or chlortetracycline. In the fourth case the patient

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had only perception of hand movements, but in the two remaining cases the results were better, the final vision in each being 6/20.

In 1952, in an excellent and comprehensive paper on the therapy of intraocular infection, Leopold [10] described six cases of penetrating intraocular foreign bodies. In one of these cases infection was present before the object was extracted. Chloramphenicol was administered both intravitreally and systemically in this case. In the other cases infection developed within 24 hours after operation. Cultures were negative in all five cases, showing again that such studies are of no practical value in diagnosing the cause of the infection or in selecting the antibiotic to be used.

In five of these six cases there was final loss of vision. The only successful case was one in which penicillin and sulfadiazine were administered systemically in massive dosages. Leopold thought that in the unsuccessful cases the dosage schedule of penicillin had not been adequate to obtain good intraocular levels.

In five other cases reported in this same communication,[10] infection appeared 24 hours after cataract extraction. In two cases the infection was not controlled and evisceration was eventually necessary; one patient was treated by penicillin and streptomycin, and the other, by these drugs plus oxytetracycline and polymyxin. In two cases excellent results were obtained by the administration of chloramphenicol by the routine just mentioned (3 gm. initially, 0.5 gm. every four hours). In the remaining case the end-result was also good; treatment consisted of injections of oxytetracycline into the anterior chamber and the administration of penicillin and streptomycin by the systemic and subconjunctival routes.

As the result of this clinical and experimental experience, Leopold [10] recommended prophylactic therapy by antibiotics, preferably chloramphenicol, both before the extraction of a foreign body and before cataract surgery. If infection should develop, penicillin and streptomycin should be employed in massive doses, both systemically and subconjunctivally, and chloramphenicol should be used in massive doses systemically. If these measures were unsuccessful, one or the other of these antibiotics should be used in tolerated doses intravitreally, as a last resort. Leopold emphasized the importance of early treatment and pointed out, as already noted, that one cannot be guided by cultural studies because of the urgency of the time element and the difficulty of obtaining positive cultures.

In the 1653 cataract extractions which he performed between 1947 and 1952, Callahan [11] had five cases of panophthalmitis, 0.3%. The organism was identified in four instances. Although the globe was salvaged in two cases, neither patient had useful vision. Chloramphenicol was used orally in large doses in one case, but enucleation was finally necessary.

Callahan regarded preoperative cultural studies as extremely important and thought that more attention to them might have prevented the loss of sight in the cases just described. For cases in which panophthalmitis developed, he recommended paracentesis, cultural studies of the aqueous, and lavage of the anterior chamber with a combination of wide-spectrum antibiotics. In spite of his failure with chloramphenicol in the case in which he employed it, he approved Leopold's recommendation of it.

Locatcher-Khorzao and Gutierrez [12] also emphasized the need for preoperative cultures before cataract extraction. They pointed out the important role of Micrococus pyogenes var. aureus (Staphylococcus aureus) in postoperative infections and mentioned the increasing resistance of this organism to the newer antibiotics.

Pearlman [13] achieved excellent results by the prophylactic subconjunctival administration of penicillin and streptomycin after cataract extraction.

Tetracycline.—When tetracycline was introduced, a new and effective broad-spectrum antibiotic became available to ophthal-

mologists. Its field of activity is about the same as that of chloramphenicol, and it has the added advantage that the depression of the bone marrow which may occur with the latter agent apparently does not occur with it.

Abraham and Burnett,[14] working with rabbits, showed that, although tetracycline systemically administered achieves better intraocular penetration than either chlortetracycline or oxytetracycline, penetration is less good with it than with chloramphenicol. When, however, they employed the massive dosage schedule suggested by Leopold for chloramphenicol, they obtained plasma and aqueous levels entirely adequate for the control of intraocular infection. In view of the absence of deleterious effects on the blood marrow when tetracycline is used, these observers concluded that this is the drug of choice both for prophylactic purposes and to combat unidentified organisms or organisms not known to be sensitive to chloramphenicol.

Hallet and his associates,[15] also working with rabbits, arrived at about the same conclusions. All their studies with tetracycline were by the intravenous route; they did not test oral administration.

Corticosteroid Therapy.—The usefulness of the corticosteriods in inflammatory conditions of the eye is now generally recognized. They reduce the inflammatory response, thus preventing tissue destruction and giving the antibiotics time to eliminate the causative bacteria. This makes them of particular value in endophthalmitis, in which vitreal infection, with the extensive inflammatory response which it causes in the choroid and retina, may produce rapid destruction of these tissues before antibiotic therapy can become effective.

Leopold[10] used cortisone in four of the five cases of intraocular infection following cataract extraction which he reported in 1952. Administration was in 100 mg. doses once daily or every eight hours after operation, with the objective of reducing the traumatic uveitis. He believed that this regime accomplished this result, but he questioned whether this form of therapy is altogether beneficial, in view of Cook and MacDonald's[16] demonstration that cortisone may also reduce the permeability of the blood-aqueous barrier, which, as already pointed out, is increased in the presence of infection. This is not a matter of great consequence when chloramphenicol and the sulfonamides are used, since they readily penetrate the normal eye, but the inhibitory effect of cortisone upon penicillin, which permeates the normal eye poorly, may greatly reduce its usefulness.

In 1955, Maylath and Leopold[17] tested the merits of cortisone alone, of antibiotics alone, and of both agents in combination in the treatment of experimental intraocular infection. Their results indicated that simultaneous treatment with cortisone and the antibiotics in massive dosages produces better results in acute infection than antibiotic therapy alone. Inflammation was attenuated in animals thus treated in comparison with its manifestations in control animals and in animals treated only with antibiotics. These observers emphasized, however, that the most important consideration of treatment was that the infecting organism be sensitive to the antibiotic selected.

Leopold[18] has recently recommended, as the most desirable regimen in intraocular infection, the administration of an appropriate antibiotic as soon as the diagnosis is made, followed by another antibiotic in combination with corticotropin (ACTH) if there is no improvement within 24 hours.

Report of Cases

Between 1948 and 1956, in the course of 740 cataract extractions, I encountered 5 cases of endophthalmitis. The incidence, 0.65%, is in accord with the incidence in most recent series. I operated on all of these patients personally, and I am quite certain that the postoperative infections could not be attributed, in any instance, to any evident break in the aseptic technique.

Essential Data in Three Cases of Endophthalmitis Following Intracapsular Cataract Extraction

Sex	Age, Yr.	Systemic Findings	Onset, Days	Management	Visual Outcome
M	51	Abscessed tooth, diabetes uncontrolled at onset	15	Atropine drops t. i. d., chloramphenicol drops and hydrocortisone drops q. 1 hr.	20/30
F	67	Cachexia	5	I. V. typhoid; after 5 injections, oral hydrocortisone 60 mg. q. 8 hr., oral chloramphenicol 2 gm. initially, 1 gm. q. 4 hr. Atropine and chloramphenicol ointments once daily Oral chloramphenicol 2 gm. initially, 1 gm. q. 4 hr.; oral hydrocortisone 100 mg. q. 8 hr.	20/25
F	72 *	Cholelithiasis, chronic colitis, cachexia	16	Atropine drops t. i. d., chloramphenicol and hydrocortisone drops q. hr. Tetracycline 3 gm. initially, 1 gm. q. 4 hr.; prednisone 25 mg. q. 8 hr.	Finger count 2 ft., retinal detachment

* Vitreous loss occurred in this case.

Preoperative cultures and prophylactic antibiotic therapy were not employed routinely in this series. Both measures were used, however, in the few cases in which there was clinical evidence, before operation, of conjunctivitis or blepharitis. None of the cases in which endophthalmitis appeared after operation were included in this small group.

In two of the five cases of intraocular infection, managed, respectively, in 1951 and 1952, the end-result was phthisis bulbi. In the light of present knowledge, it is clear that the dosages of penicillin and chloramphenicol which were employed were not adequate.

In two of the three other cases, treated, respectively, in 1954, 1955, and 1956, the outcome was happier (Table). In each instance treatment was instituted immediately after endophthalmitis appeared in the form of a vitreous abscess. Initial improvement was evident within 24 to 48 hours after therapy was begun, and in the course of 2 or 3 weeks the vitreous gradually cleared. The oral dosages of both the antibiotics and the corticosteroids were gradually diminished as the eye quieted down and vitreous clearing became evident.

In the remaining case treatment was along the same lines, but the final vision was limited to finger count, not, it was believed, because of the intraocular infection but because of a retinal detachment, which was probably related to loss of vitreous at operation.

Comment

To date, as this review shows, only a limited number of cases are on record in the literature in which endophthalmitis complicating cataract extraction has been treated successfully. With the advent of the newer antibiotics, the prognosis seems somewhat improved, but only if treatment is begun early and only if the appropriate antibiotic is used in adequate dosages.

Either chloramphenicol or tetracycline is the antibiotic of choice, since both have the ability to penetrate through the blood-aqueous barrier when they are given in massive dosages. Both have broad antibacterial spectra, and both are effective when administered orally.

The use of a corticosteroid with the antibiotic is recommended, as it will produce a rapid diminution of the inflammation and thus prevent the destruction of the retina and choroid. This recommendation is in line with Leopold's [18] recent demonstration that antibiotic therapy alone may control the infectious agent but that vision may be lost as the result of the severe inflammatory reaction.

With the increasing resistance of strains of Staphylococcus to the newer antibiotics, the use of combinations of antibiotics, such as Sigmamycin (a mixture of oleandomycin and tetracycline), may be of great value in the treatment of postoperative endophthalmitis.

Summary

In spite of the more encouraging outlook offered by the use of the newer antibiotics in postoperative endophthalmitis following cataract extraction, this is still a complication greatly to be feared.

The best results are achieved if treatment is begun early. An appropriate antibiotic must be selected and must be employed in adequate dosages. At present, chloramphenicol and tetracycline are the agents of choice; both are broad-spectrum antibiotics and both have the ability to penetrate the blood-aqueous barrier when they are given in massive dosages.

A corticosteroid is often useful in controlling the inflammatory reaction, and thus preserving vision, until antibiotic therapy can control the infection.

Five cases of endophthalmitis following cataract extraction are reported. Two cases, treated before chloramphenicol and tetracycline were available, were absolute failures. One patient, treated with chloramphenicol, tetracycline, and prednisone, had vision limited to finger count because of a retinal detachment probably related to the loss of vitreous at operation. The other two patients, treated with hydrocortisone and massive doses of chloramphenicol by mouth, had excellent final vision.

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The Surgery of Cataract in Megalocornea

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In an account of the removal of a cataract in a case of megalocornea by Smillie (1955), it was suggested that, since instances of such surgery are rare and the results are uncertain, further experiences should be recorded. A further two cases are therefore submitted, both involving one patient.

Megalocornea is a bilateral developmental anomaly in which the anterior segment of the globe is larger than normal. The absence of a raised intraocular pressure and its pathological sequelae is a notable feature which differentiates the condition clearly from buphthalmos. In his classical "Treatise on Glaucoma" Elliott (1922) described the condition as "a product of overgrowth, not of overstretching." The most prominent feature of megalocornea is an enlargement of the circumference of the cornea, but the changes are not limited to this tissue. Atrophy of the iris may occur, with fragility and even rupture of the zonule. Iridodonesis is seen not infrequently; the lens may be tremulous and subluxated. Cataractous changes are not uncommon. Operation, however, has not been accompanied with unvarying success.

Before 1931, in 18 extractions in cases of megalocornea, though 12 attained useful vision, vitreous was lost in 7 cases and 11 lenses had to be delivered with a spoon. Three of these had postoperative retinal detachments.[4]

Since 1931, in 10 extractions in cases of megalocornea useful vision resulted in 9, one eye was lost postoperatively, and there was loss of vitreous in 2 cases.[2]

One must agree very definitely with Duke-Elder that "operation should not be undertaken light-heartedly," and in the two cases recorded below surgical intervention was decided upon with a good deal of misgiving.

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Report of Two Cases in One Patient

Both extractions were performed on one patient, with an interval of 10 months between operations.

A 39-year-old crane driver was first seen in private practice in April, 1954, complaining that the vision had failed in each eye, especially in the left.

Past History.—The patient had always had good sight, and, apart from a blow in the left eye with an acorn at the age of 9, there had never been any eye trouble.

Family History.—He was an only child, and as far as he knew there was no family history of bad eyesight.

General Health.—He was a thick-set healthy man of good physique and ruddy complexion, with thick prematurely gray hair. The urine was free of sugar and albumin. The blood pressure was within normal limits.

Ocular Examination.—Vision: O. D., 6/12, correcting to 6/6 with a −0.25 D. sphere; O. S., hand movements at 6 ft.

Both eyes appeared larger than average: The right cornea measured 15 mm. in diameter; the left cornea, 16 mm. Both corneas were clear. The anterior chambers were deep, and the pupils reacted to light, the left less briskly than the right. The pupillary apertures in moderate room illumination seemed rather smaller than average and were about 3 mm. in diameter. They dilated poorly with 2% homatropine and cocaine drops and after three instillations widened only to 6 mm. There was bilateral iridodonesis. The lenses were tremulous and cataractous. On the right side the posterior cortex was chiefly involved with a central star-shaped opacity, while further forward were seen scattered polychromatic dots. The fundus was normal. The left fundus was

obscured by extensive lens changes involving the posterior half, while anteriorly could be seen many fine polychromatic granules. The intraocular tension was 20 mm. Hg (Schiøtz), right and left.

Owing to the uncertain prognosis of operation, the patient was advised to seek a less exacting job and to report at three-month intervals for observation.

He reappeared a year later at St. Vincent's Hospital, Melbourne. The left cataract was denser, and the eye was divergent about 10 degrees. The vision of the right eye was 6/12. It was noted with interest that he had continued to operate a mobile crane without mishap.

After a further six months the vision of the right eye had diminished to 6/24, and operation was sought to enable him to gain a living. The left cataract was removed first.

Hospital Courses.—An intracapsular cataract extraction was performed with the aid of a Bell erysiphake, with use of local anesthesia. A retrobulbar injection of 2% procaine (Novocain) was given, and akinesia of the lids was secured with the aid of 5 cc. of 2% procaine injected according to the Van Lint technique. A black 0000 non-absorbable surgical (silk) suture was placed through the superior rectus tendon, and a corneoscleral suture (000000 silk) of the Stallard type was placed with the aid of a Grieshaber needle. A Graefe knife section was made, with a small conjunctival flap. At this stage the speculum was removed, as the iris appeared to move forward. The Bell erysiphake was then applied to the lower half of the lens, and after some two minutes' wait, to allow the lens to "mould" into the suction cup, it was gently tumbled out. Vitreous presented in the lips of the wound, and it seemed wise to complete the iris toilet without iridectomy. A drop of 0.5% physostigmine (eserine) was instilled, and a double pad was applied.

The postoperative stay in hospital was complicated by the somewhat boisterous behavior of the patient, who inadvertently struck himself in the eye twice and had hyphema on the 8th and again on the 10th postoperative days. The blood absorbed rapidly, and the eye settled down by the 14th day. It was noted that the pupil was just a little drawn up at 12 o'clock.

Four weeks later the patient reported with a painful red right eye. The tension was raised (60 mm. Hg, Schiøtz), and the cornea was steamy. Pilocarpine nitrate 1% drops were instilled every four hours, and after seven days the tension was normal. One month later vision was 6/6, with $+5.0/+3.0\times170$.

Ten months later the right cataract was removed. This time lid sutures were used instead of the speculum. In consideration of the difficulties with the right eye, a small pheripheral iridectomy was done at 12 o'clock. Once again the lens moulded well into the suction cup of the erysiphake, but the pupil took some four minutes to dilate, and the lens slipped off the cup as it was being delivered. It was retrieved intact when suction was reapplied, and though the vitreous came forward none was lost. Physostigmine was instilled, and at the end of the operation the pupil was round.

Despite repeated warnings, the patient was still overactive, and he had a small hyphema on the fourth day. This time there was no rise in tension, and two months later vision was 6/9, with $+5.5/+2.5\times180$. He has remained well since, and after two years he still drives the mobile crane with dexterity.

Comment

In these two extractions the erysiphake appeared well adapted to the peculiar circumstances, in that these lenses, though mature, seem to have tough mobile capsules which mould well.

Although both lenses were subluxated, no vitreous was lost, though on each occasion vitreous came forward to the lips of the wound.

The avoidance of pressure on the globe, either by using lid sutures or by removing the speculum after the section, seemed es-

sential. I have not had experience with the Arruga type of speculum.

Dr. K. J. O'Day, Honorary Ophthalmic Surgeon to St. Vincent's Hospital, Melbourne, gave assistance and advice in this case and gave permission to publish the case records.

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Experimental Studies on Cx-Reactive Protein in Rabbit Aqueous

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Preliminary studies (Wolkowicz, Hallett, and Leopold [14]) on the possible role C-reactive protein might play in ocular pathology suggested that the C-reactive protein (CRP) test, when applied to the aqueous humor, may shed some additional light on the etiology and differential diagnosis of uveitis. The following data are pertinent to the present study.

C-reactive protein is found consistently in sera of patients suffering from an active inflammatory or necrotizing process, not so consistently in cases of rheumatoid arthritis, virus infection, and active tuberculosis (Roantree and Rantz [10]).

C-reactive protein, unlike the usual antibody, appears in the early stage of infection, and its titer declines when antibodies tend to appear, during the convalescing period (Perlman et al.[9]).

Comparative electrophoretic studies of CRP and antibody to C-polysaccharide showed that the former seems to migrate with the α-globulin fraction, whereas the latter is found in the γ-globulin group. Perlman et al. conclude that "whereas antibody globulin may be a reoriented normal globulin, CRP is probably an entirely new serum protein."

Wood,[7,16,17] who studied the relation between the early appearance of CxRP* and subsequent antibody production, concluded from his experiments that early formation of CxRP was consistently followed by high titers of precipitating antibodies. Logically, he suggests that "acute phase protein (CRP) might be directly concerned in the chain of events that lead to antibody formation."

Immunological studies of the aqueous humor are not new. The first important contribution can be traced as far back as 1902, when Van Dungren became convinced, as a result of his experiment, that the rabbit's eye is capable of producing antibodies in addition to those which succeed in passing the blood aqueous barrier. Since then, a voluminous literature on this subject has been accumulated. While all this work had, unquestionably, a profound influence on our present knowledge of the immunological properties of the aqueous, only the work of Witmer [13] and of Goldmann and Witmer [4] has a direct bearing on the present studies. Their experiments showed that less than a third of the total amount of Leptospira-agglutinating antibodies present in the serum will pass the blood-aqueous barrier in a normal eye. This proportion will be the same in the secondary aqueous, thus proving that an altered blood-aqueous barrier still retains some of its selective power. The antibody titer in the aqueous of an infected rabbit's eye, as a rule, increases with the severity of the infection and may surpass that of the serum. The most likely explanation is the ability of antibody production in situ, which, Witmer believes, is coincident with the appearance of infiltrating plasma cells and lymphocytes in the uvea.

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*CxRP is a homologous protein appearing in the rabbit blood stream under similar conditions as CRP in the human blood. CxRP designation stems from its ability to precipitate a Cx-polysaccharide in the same manner as the human CRP precipitates the C-polysaccharide.

The present experiments were undertaken to demonstrate (1) the passage of CxRP through the blood-aqueous barrier and (2) the formation of CxRP within the eye and to establish (3) the value of the CxRP test in the aqueous humor in experimental uveitis.

Material and Methods

The animals used in all the ensuing experiments were healthy rabbits weighing between 4 and 5 lb. As a rule, five rabbits were used for each phase of the experiment; occasionally a few more were added if the results were equivocal. Each rabbit was tested for presence of CxRP in blood serum prior to the start of the test. Surprisingly, quite a few healthy-looking rabbits having a positive CxRP in the serum were usually found in each batch. Those rabbits were rejected except in the first part of the study, when they were purposely retained for comparative studies. Experimental uveitis in the rabbit's eye was produced by a technique previously applied to our pilot studies and originally described by Foss.[1] The material to be tested was introduced in the amount of 0.1 cc. intravitreally through a 26-gauge needle. In some experiments, where additional information could be obtained by depositing the inoculum in the anterior chamber, the puncture was made near the limbus and the content of the syringe was thoroughly mixed with the aqueous by moving the plunger of the syringe back and forth several times. In order to eliminate secondary contamination the rabbit's eyes were treated for 24 hours prior to the inoculation with several applications of an antibiotic ointment containing bacitracin, neomycin, and polymixin B (Neosporin) and the site of the injection was touched with tincture of iodine. The aspirated aqueous, at the completion of the experiment, was routinely cultured, and all the eyes suspected of contamination were rejected.

The occasional difficulties which one encounters in obtaining a sufficient amount of blood from the venipuncture of a rabbit's ear have been largely overcome by applying the "finger tip technique" originally described by Goldin and Kaplan.[3] † The test involved the collection of blood in a capillary tube of 1.5 mm. bore and 90 mm. in length after pricking the marginal vein of the rabbit's ear. The small amount of serum obtained by this method is amply sufficient for our purpose. Our standard technique of the CxRPA test is essentially the same as that described in our preceding report. We abandoned the use of the incubator and kept the tubes in room temperature. This simplification, we feel, also helped to pack the precipitate column. Sheep antiserum, made available to us by Dr. H. F. Wood, was used in all our animal experiments. The potency of the antiserum was repeatedly tested and found to be uniformly stable. The sampling of the aqueous humor was done in the usual manner through a 26-gauge needle or Amsler's trocar. In case of a severe uveitis where the anterior chamber was filled with fibrin and exudates, we had to make the opening with a keratome and place the capillary tube directly in contact with a visible aqueous pool. CxRP testing of aqueous was done similarly to that of serum, and the results were interpreted in the same manner. Here, a word of caution is needed. The precipitate in the aqueous often has a tendency to remain suspended through the liquid column and, if not sought for under loupe magnification, can easily pass unnoticed. It was found that centrifugation in the revolving rack helped considerably the process of "packing" the precipitate and thus making the quantitative estimate more reliable. Fibrinous, stringy exudates when present in the aqueous may enter the capillary tube and simulate flocculates of Cx-reactive protein.

† The Schieffelin Company, which supplied us with some of the material used in this study, includes the exact details and directions of the "finger tips technique" in its current CRPA test literature.

TABLE 1.—*Cx-Reactive Protein Reaction Forty-Eight Hours After Intravenous Injection of Killed Typhoid-Paratyphoid Bacilli*

Rabbit No.	CxRP Reaction to Typhoid I. V.		
	Blood Serum	Aqueous	
		Primary	Secondary *
210	1+	--	1±
233	3+	--	1+
240	3+	--	1+
250	3+	--	2+

* Secondary aqueous was aspirated one hour after the first puncture.

Experiments and Results

EXPERIMENT 1.—*Passive transfer of CxRP through blood-aqueous barrier*

One-half cubic centimeter of stock typhoid vaccine (100,000,000 killed typhoid and paratyphoid bacilli per cubic centimeter) was injected into each rabbit's blood stream. Within 24 hours a blood sample and primary aqueous of the right eye were taken simultaneously. One hour later the same eye was tapped again and approximately 0.1 cc. of secondary aqueous was aspirated. All blood serum specimens gave a positive CxRP reaction.[11] The primary aqueous samples were negative for CxRP, whereas the secondary aqueous gave a uniformly positive response. It was apparent that the degree of positivity of the secondary aqueous followed closely the CxRP titer in the corresponding serum: A strongly positive blood serum gave a strongly positive aqueous reaction, although to a smaller degree (Table 1).

As a corollary to this study, a rabbit who had a positive blood serum in the preliminary sampling was tapped for primary aqueous and secondary aqueous one hour later. Here, again, the primary aqueous showed negative reaction whereas the secondary aqueous gave a positive reaction. CxRP, like other blood serum proteins, is not present in the aqueous of a healthy eye, regardless of the blood level. It will, however, like other serum proteins, pass through an altered blood-aqueous barrier, the aqueous titer remaining below the serum level. The rate of transfer calls for further quantitative investigation.[15]

EXPERIMENT 2.—*Intraocular Cx-reactive protein formation*

One-tenth cubic centimeter of stock typhoid vaccine was injected intravitreally in the right eye of five healthy rabbits. Three days later, after it was ascertained that the aqueous exhibited an active anterior uveitis, blood and aqueous samples were taken (Fig. 1). Four rabbits had negative CxRP reaction in the blood prior to and following the inoculation. The blood of the fifth rabbit (Rabbit 255) was strongly positive before and after inoculation but was in-

Fig. 1 (Rabbit 252).—Experimental uveitis following intravitreal injection of stock typhoid vaccine. Low-power view of inflammatory reaction in prepapillary area. Cup is filled with vascularized tissue and round-cell infiltration. Very little reaction was noted in the rest of the choroid and retina.

TABLE 2.—*Results of CxRP Test in Blood and Aqueous After Intravitreal Injection of Killed Typhoid-Paratyphoid Bacilli*

Rabbit No.	CxRP Reaction to Intravitreal Injection of Typhoid					
	Before Inoculation, Blood Serum	4 Days After Intravitreal Injection of Vaccine				7 Days After Inoculation, Primary Aq., O. D.
		Blood Serum	Primary Aq.		Secondary Aq., O. S.	
			O. D.	O. S.		
251	Neg.	1+	4+	Neg.	Neg.	Neg.
252	Neg.	Neg.	4+	Neg.	Neg.	Neg.
253	Neg.	Neg.	3+	Neg.	Neg.	Neg.
254	Neg.	Neg.	1+	Neg.	Neg.	Neg.
255	4+	3+	4+	Neg.	1+	Neg.

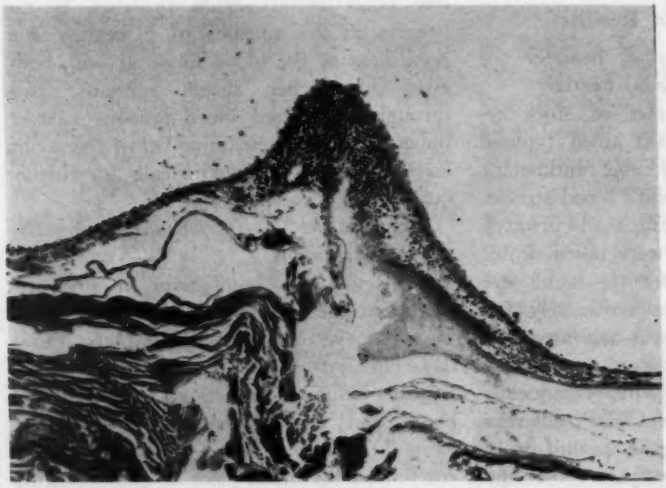

Fig. 2 (Rabbit 256).—Experimental viral uveitis. Diffuse and dense infiltration of choroid, with eruption of cells in the subretinal space.

cluded for comparative evaluation. All the aqueous specimens were strongly positive. By comparison, the aqueous in the intact left eye was consistently negative. The secondary aqueous in the left eye was also negative with the exception of Rabbit 255, which had initially a strong positive blood serum reaction; therefore, a passive transfer of CxRP occurred in this eye through an altered blood-aqueous barrier. Ten days after the intraocular injection of typhoid vaccine the right eye became quiescent and the aqueous, clear. At that time, another cameral puncture of the right eye gave a negative CxRP reaction in all five rabbits (Table 2).

We may conclude that uveitis produced by injection of killed typhoid-paratyphoid bacilli into the rabbit eye is capable of stimulating the production of CxRP in the aqueous. The stimulus did not appear strong enough to produce CxRP in the blood stream. In the one rabbit (Rabbit 251) with a positive blood serum comparative titers of blood and aqueous were strongly suggestive that Cx-reactive protein did originate within the globe. The presence of Cx-reactive protein could be detected early, at the height of the inflammation, and its disappearance coincided with the subsidence of the inflammatory process.

EXPERIMENT 3.—*CxRP in experimental viral uveitis*

An acute experimental viral uveitis was produced in the right eye of five rabbits by injection of 0.1 cc. of a suspension of herpes simplex. The culture was prepared in the following manner‡: The chorioallantoid membrane of a chick embryo, seeded with herpes virus 14 days previously and

‡ The herpes virus suspension was grown and prepared by Dr. T. W. Sery, of the Research Laboratory of the Wills Eye Hospital.

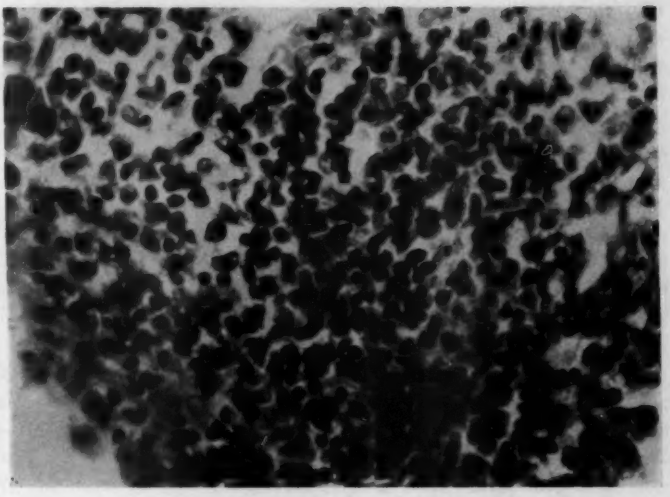

Fig. 3.—Higher magnification of Figure 2. The same section, showing large- and small-cell inflammatory reaction in choroid.

showing the typical pock-marks of a successful growth, was separated, ground with sand, and suspended in isotonic saline solution. The supernatant fluid was then injected into the rabbit's eye. For control eyes a healthy chorioallantoid membrane was ground in the same manner and the suspension was injected intravitreally. Both suspensions had been cultured for bacterial sterility prior to the inoculation. All the virus-infected eyes developed acute uveitis, which reached its peak on the fourth day. Aqueous flare of variable intensity was usually noticeable. There were flaky deposits on the lens capsule and a few synechiae (Figs. 2 and 3). Blood and aqueous samplings were taken on the same day. All five rabbits had a positive CxRP reaction in the blood serum. All aqueous specimens showed also a positive CxRP reaction. The intact left eye, which showed no inflammatory activity throughout the experiment, when tapped gave a negative reaction in the primary aqueous and a very strong positive reaction in the secondary aqueous (Table 3).

TABLE 3.—*CxRP in Rabbit Blood Serum and Aqueous After Intravitreal Injection of Herpes Simplex Virus in the Right Eye**

Rabbit No.	CxRP Reaction to Intravitreal Herpes Simplex				
	Before Inoculation,	4 Days After Inoculation			
	Blood Serum	Blood Serum	Primary Aq.		Secondary Aq. O. S.
			O. D.	O. S.	
256	Neg.	1+	2+	Neg.	5+
257	Neg.	1+	1+	Neg.	5+
258	Neg.	1+	1+	Neg.	2+
259	Neg.	1+	2+	Neg.	5+
260	Neg.	1+	2+	Neg.	3+

* The strong positive reaction in the secondary aqueous of the intact eye (as compared with O. D.) is strangely reminiscent of sympathetic ophthalmia.

The control eyes inoculated with a normal chorioallantoid suspension remained white throughout the time of the experiment, and their blood serum as well as aqueous remained negative for Cx-reactive protein. At the end of two weeks the infected eyes were enucleated; the vitreous was deposited on a healthy chorioallantoid membrane, where after 48 hours the typical pock-marks of herpes simplex appeared. Some of the vitreous was then mixed with equal parts of glycerin and deposited on a scarified rabbit's cornea. We were, however, unable to reproduce by this method a herpetic ulcer. In addition to uveitis, one of the rabbits exhibited a paralysis of its hindlegs, which slowly subsided.

One may conclude that herpes simplex virus is capable of producing an acute uveitis in the rabbit's eye, with tendency to a slow resolution. The virus, in all likelihood, stimulates Cx-reactive protein formation in the infected eye, if one may judge by the

Fig. 4 (Rabbit 264).—Horse-serum-induced experimental "primary anaphylactic uveitis." Inflammatory reaction of ciliary body, posterior chamber, and anterior vitreous. Note the uniform large-round-cell infiltration.

TABLE 4.—*Summary of CxRP Findings in "Primary Anaphylactic Uveitis"*

Rabbit No.	CxRP Reaction to Intravitreal Horse Serum		
	Before Inoculation, Blood Serum	After Inoculation	
		Blood Serum	Primary Aq., O. D.
264	Neg.	Neg.	Neg.
270 *	Neg.	Neg.	3+ (?)
281	Neg.	1+	±
283	Neg.	Neg.	Neg.
264	Neg.	Neg.	Neg.

* The strong aqueous reaction in Rabbit 270 is not clear in view of the fact that slit-lamp examination prior to cameral puncture showed very little reaction.

stronger reaction in aqueous than in serum. The positive reaction in the blood should be viewed as a spread of the virus into the blood stream, with the ensuing systemic response. Witness to this is the severe diarrhea and paraplegia of one of the rabbits. It would be difficult to assume that the infected eye is producing the CxRP in such large quantities as to create a detectable blood level. The significance of a strong positive reaction (as high as 5+) in the

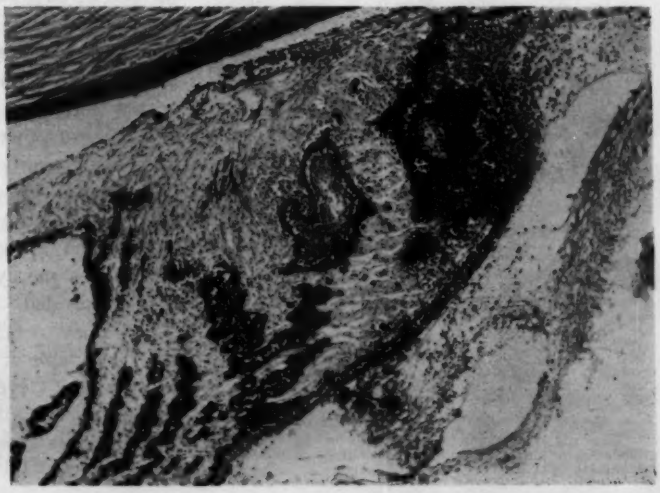

Fig. 5 (Rabbit 273).—Horse-serum-induced experimental uveitis. Intravitreal injections of horse serum in a sensitized animal. Infiltration of anterior vitreous and angle similar to "primary anaphylactic uveitis" (compare with Fig. 4). Edema of ciliary body is more prominent.

TABLE 5.—*CxRP Reactions in Rabbits Sensitized with Horse Serum* *

Rabbit No.	CxRP Reaction to Horse Serum in Sensitized Animals		
	Before Injection, Blood Serum	2 Days After Intravitreal Injection	
		Blood Serum	Primary Aq., O. D.
271	Neg.	Neg.	1+
272	Neg.	1+	Neg.
273	Neg.	2+	1+
274	Neg.	Neg.	Neg.
275	Neg.	3+	1+

* The rabbits were sensitized with two subcutaneous injections of 1.0 cc. of horse serum at the 10th and 5th days prior to intravitreal injection.

secondary aqueous of the control eye is not quite clear. Would a passage of the virus through an altered blood-aqueous barrier be responsible for this anomaly?

EXPERIMENT 4.—*CxRP in horse-serum-induced experimental uveitis*

This phase of the study was concerned with experimental uveitis produced by horse serum. The animals were divided into three groups. The first group received 0.1 cc. of horse serum intravitreally in the right eye. On the seventh day they usually showed a "primary anaphylactic iridocyclitis," consisting of a discrete aqueous flare and a few "floaters" (Fig. 4). According to Foss,[1] the eye becomes sensitized to the remaining particles of horse serum which are not yet absorbed from the vitreous. Rabbit 281, at the end of seven days, showed 1+ CxRP reaction in the blood and a trace in the aqueous. Rabbit 270 showed a negative blood response and a strong aqueous reaction; the rest were negative (Table 4).

The second group received two subcutaneous injections of 1 cc. of sterile horse serum at weekly intervals. Two weeks after the last injection 0.1 cc. of the horse serum was injected into the vitreous of the right eye, and three days later blood and aqueous specimens were taken. In this group the uveal reaction was more evident; in addition to the aqueous flare, dust-like deposits on the capsule could be seen and there were a few posterior synechiae (Fig. 5). Two sera were negative for CxRP; one was faintly positive, and two, strongly positive. The aqueous reactions were negative with the exception of two. Those two eyes, which belonged to the rabbits exhibiting a strong serum reaction, showed a weakly positive response (Table 5).

The third group was sensitized in the same manner as the previous group. The shocking dose, however, was introduced intravenously a week after the last subcutaneous injection. Forty-eight hours later all blood samples were positive for CxRP. The aqueous from the right and left eyes was aspirated and was found to be free of Cx-reactive protein. After one week, another blood sampling showed that one serum still remained positive. At this time, 0.1 cc. of horse serum was injected into the right vitreous. Six days later, anterior chamber puncture of the right eye revealed a uniformly positive CxRP reaction (Table 6). Clinically the uveitis picture differed very little from that of the previous group (Fig. 6).

The conclusions to be drawn from those experiments must be of necessity partly presumptive and speculative. In spite of a substantial number of rabbits tested in this study, the number of animals assigned to each phase of it is too small for statistical evaluation. The results, however, suggest that the so-called "primary anaphylactic

TABLE 6.—*CxRP Reactions in Rabbits Given Intravitreal Injections of Horse Serum After an Intravenous Shocking Dose*

Rabbit No.	CxRP Reaction to Intravitreal Horse Serum in a Sensitized Animal						
	Before Injection, Blood Serum	2 Days After Shocking Inj., I. V.			1 Wk. After I. V. Injection, Blood Serum	6 Days After Intravitreal Injection	
		Blood Serum	Primary Aq.			Blood Serum	Primary Aq., O. D.
			O. D.	O. S.			
285	Neg.	1+	Neg.	Neg.	Neg.	Neg.	2+
286	Neg.	2+	Neg.	Neg.	1+	2+	1+
288	Neg.	1+	Neg.	Neg.	±	±	3+

Fig. 6 (Rabbit 285).—Horse-serum-induced experimental uveitis. Intravitreal injection of horse serum following intravenous shocking dose. Section shows intense inflammatory reaction of ciliary body. Disc in same section shows intense prepapillary inflammation.

uveitis" (a single horse serum injection acting as a sensitizing and shocking dose) is not an adequate stimulus for CxRP appearance.

The result of the second portion of the experiment suggests that the standard multiple-dose sensitization will render the animal's blood serum CxRP-positive, whereas the involved eye will show a parallel response but to a smaller degree.[5,6] To all appearances the eye behaves as if the intracameral injection merely altered the blood-aqueous barrier, permitting the passage of CxRP into the anterior chamber. This is the titer one would expect in the secondary aqueous of a serum-positive healthy eye.

The third phase of the experiment considers a highly sensitized animal who recovered from an anaphylactic shock. An intracameral injection produced a marked response, and a comparison with its corresponding serum leaves no doubt that CxRP was produced within the globe.

EXPERIMENT 5.—*CxRP in pyogenic experimental uveitis*

Part of the studies dealt with the two commonest pyogenic organisms: Streptococcus pyogenes and Micrococcus pyogenes var. aureus (Staphylococcus aureus). The culture was introduced intravitreally in 0.1 cc. of isotonic saline solution and, in the second phase of this experiment, into the anterior chamber. The number of organisms was kept at the level of 100,000,000 per cubic centimeter; the commerically available typhoid-paratyphoid suspension was used as a standard for comparison in the Klett apparatus.

1. Twenty-four hours after the onset of pyogenic endophthalmitis produced by Streptococcus pyogenes all the blood and aqueous reactions were positive for CxRP. The clinical picture was fairly uniform, with slight individual variations, i. e., iris congested, aqueous showing a fairly dense flare, fluffy deposits on the lens capsule. Five days later the individual variations became more accentuated; some eyes cleared, while others still presented a picture of an acute uveal reaction. At this time, only two blood and three aqueous specimens were positive. Two weeks after the onset, when all eyes became quiescent, with only an occasional aqueous floater, all blood and aqueous samplings became negative. Cultures taken the same time as the cameral punctures were all sterile.

The clinical picture of an experimental Streptococcus uveitis as observed in this experiment is variable. The intensity, duration, and outcome depend, to a great extent, on the virulence, number of organisms in-

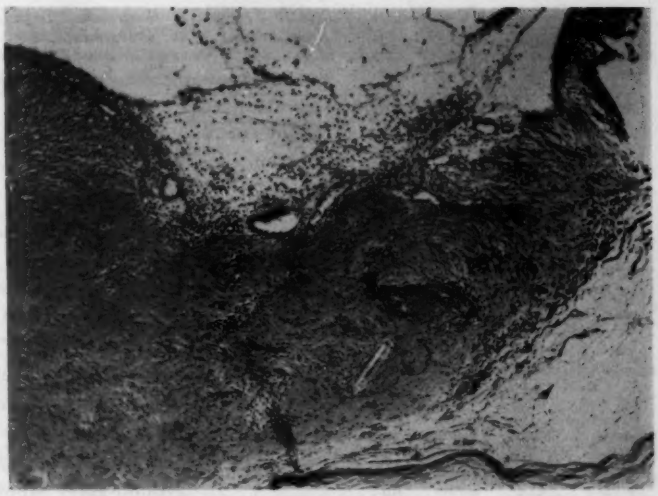

Fig. 7 (Rabbit 277).—Pyogenic experimental uveitis following intravitreal injection of Streptococcus pyogenes. Pyogenic reaction with predominence of polynuclear cells in deep vitreous and prepapillary area.

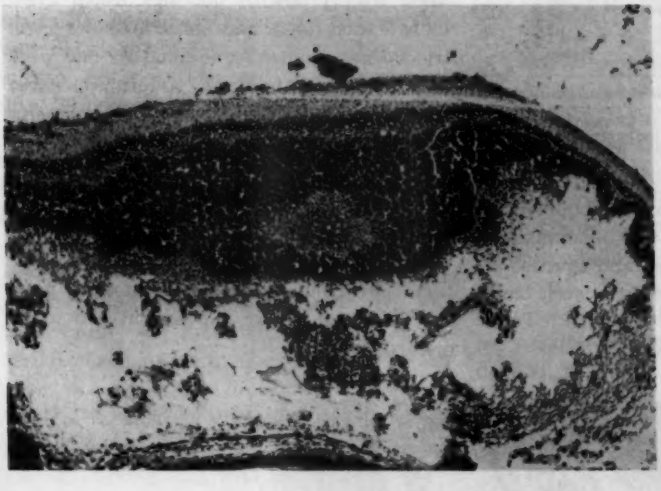

Fig. 8.—Streptococcal endophthalmitis, showing a retinal abscess with a necrotic center.

troduced, and receptivity of the animal (Figs. 7 and 8). The strain used in this study was chosen because of the moderate and uniform reaction it produced, making possible more consistent observations. It is obvious from this experiment that Streptococcus can provoke the appearance of CxRP in the blood and in the aqueous 24 hours after injection. Since the titer, from the start, is the same in the aqueous and in the blood and since later on the aqueous exceeds by far the blood level, one can safely assume that the CxRP is being produced locally within the globe. The positive blood reaction would be, then, the result of an early mild septicemia. Here it is interesting to note, as we have done previously,[14] the remarkable barrier formed by the lens-zonule-ciliary body to bacterial penetration into the anterior chamber. While this was not true with other bacterial cultures, for this particular strain the barrier was 100% effective. On the fifth to sixth day the systemic reaction, having dealt effectively with the invading organisms, subsided promptly (two out of five rabbits still had

TABLE 7.—*Results of CxRP Test After Intravitreal Injection of 10,000,000 Organisms of S. Pyogenes*

Rabbit No.	CxRP Reaction to Intravitreal S. Pyogenes						
	Before Injection, Blood Serum	24 Hr. After Injection		1 Wk. After Injection		2 Wk. After Injection	
		Blood Serum	Primary Aq., O. D.	Blood Serum	Primary Aq., O. D.	Blood Serum	Primary Aq., O. D.
276	Neg.	2+	1+	Neg.	3+	Neg.	Neg.
277	±	1+	2+	Neg.	1+	Neg.	Neg.
278	Neg.	1+	1+	Neg.	Neg.	Neg.	Neg.
279	Neg.	2+	2+	1+	5+	Neg.	Neg.
280	Neg.	1+	2+	2+	Insufficient amount	Neg.	Neg.

TABLE 8.—*Results of CxRP Test After Intravitreal Injection of 10,000,000 Organisms of M. Pyogenes Var. Aureus* *

Rabbit No.	CxRP Response to Intravitreal M. Pyogenes Var. Aureus			
	Before Injection, Blood Serum	48 Hr. After Injection		1 Wk. After Injection, Primary Aq., O. D.
		Blood Serum	Primary Aq., O. D.	
306	Neg.	2+	5+	3+
307	Neg.	4+	2+	5+
308	Neg.	4+	3+	5+
309	Neg.	5+	1+	Strongly pos.

* These observations were of shorter duration than those of the Streptococcus series. The eyes would burst spontaneously one week after inoculation. Thus, the CxRP reaction in the last aqueous specimen of Rabbit 309 could not be properly estimated.

blood serum positive for CxRP), whereas the aqueous showed a reaction commensurate with the intensity of the inflammation, from negative to 5+. Blood and aqueous of all the rabbits became negative a week later, when all signs of uveitis subsided (Table 7).

2. The injection of 0.1 cc. of a suspension of M. pyogenes var. aureus (100,000,000 organisms per cubic centimeter) was followed by a severe inflammation. Typically, three to four days after the onset there was marked chemosis; the cornea took on a ground-glass appearance; the pupil was filled with yellowish floccules which gradually settled down and obliterated the lower iridocorneal angle. At the end of one week the eye became hard, the anterior chamber deepened, and the iris structure became poorly visualized. At this stage the eye would burst spontaneously or at the slightest attempt to penetrate the anterior chamber with the needle. CxRP could be detected in the aqueous 24 hours after the inoculation. The reaction remained strongly positive until the eye or the animal had to be discarded (Table 8).

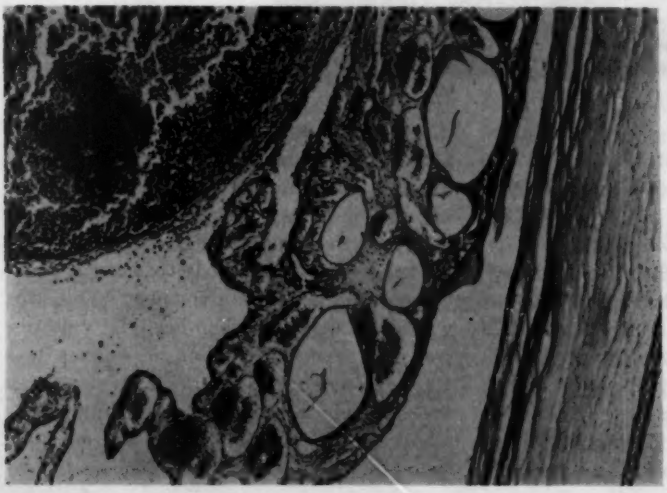

Fig. 9 (Rabbit 330).—Section showing severe iritis resulting from intracameral injection of micrococci. Notice extreme iris edema and abscess formation in the posterior chamber.

TABLE 9.—*Results of CxRP Test in Blood and Aqueous as Compared with Aqueous Cultures*

Rabbit No.	CxRP Response to Intracameral M. Pyogenes Var. Aureus			
	Before Injection, Blood Serum	24 Hr. After Injection		
		Blood Serum	Primary Aq., O. D.	Aqueous Culture
320	Neg.	3+	3+	Little growth
321	Neg.	Neg.	Neg.	Approx. 25 colonies
326	Neg.	Neg.	Neg.	Dense growth
330	Neg.	5+	1+	Neg.
331	Neg.	8+	±	Neg.
332	Neg.	8+	±	Neg.
324 *	Neg.	3+	Neg.	Mod. growth

* Rabbit 324 had, two days later, a positive CxRP reaction in the blood and aqueous, whereas aqueous culture became sterile. Two weeks later the eye recovered, and both aqueous and blood became CxRP-negative.

In order to find out whether an inflammatory aqueous is CxRP-positive in the presence of living organisms, seven additional rabbits (right eyes only) were inoculated with the same Micrococcus culture, the bacterial suspension having been introduced into the anterior chamber. The clinical picture, 24 hours later, was an intense anterior uveitis with profuse conjunctival discharge and corneal edema. The pupillary opening was filled with yellowish fluffy exudate adherent to the lens capsule (Fig. 9). By comparing Table 8 and Table 9, which summarize the results of intravitreal and intracameral inoculations, respectively, one can readily see that, while all the blood serum reactions, with one exception, were strongly positive, the aqueous was negative in three rabbits, questionable in two rabbits, and strongly positive in one rabbit. If one correlates those data with the respective cultures, there appears to be some inhibitory action of the living bacteria on the production of CxRP. It is interesting to note that Rabbit 324, which overcame the intracameral infection, had a negative aqueous reaction 24 hours after inoculation, at the height of uveitis, when the culture showed numerous Micrococcus colonies. Two days later, when another tapping showed a sterile aqueous, the reactions for CxRP became positive. Two weeks after the onset, when the uveitis subsided, blood and aqueous became negative and the culture became sterile.

EXPERIMENT 6.—*CxRP in P. P. D.-induced and tuberculous experimental uveitis*

This phase of the studies dealt with experimetnal uveitis produced with tuberculin purified protein derivative (P. P. D.) and live tubercle bacilli.[18-20] Five strains of avirulant tubercle bacilli kept on Trudeau medium were made available to us by Dr. Joseph D. Aronson, of the Henry Phipps Institute, Philadelphia. They have been designated, respectively, as JH4, JH16, JH6, BCG, and H37RM.

1. Six rabbits were selected for the first part of this experiment. Three rabbits received an intravenous injection of 0.002 mg. of tuberculin P. P. D., and the remainder received 0.05 mg. At the end of six weeks blood serum was examined and found to be free of CxRP. One-tenth cubic centimeter of the same P. P. D. solution was then injected intravitreally, care being taken to use the same concentration with which the rabbit was originally sensitized. The uveitis which followed was mild and could be detected only by slit-lamp microscopy. The changes observed consisted of narrowing of the anterior chamber, an occasional fibrinous membrane, and a few lens opacities (Fig. 10). The aqueous samplings were all negative for CxRP. One blood serum sample became strongly positive; the rest remained negative. Six weeks later 0.1 cc. of the same solutions was injected in the anterior chambers of the sensitized rabbits. Blood and aqueous examined 48 hours later showed no trace of CxRP. (Table 10).

2. In the second part of this study each of five rabbits was inoculated with a saline suspension of one of the five strains of tubercle bacilli intravitreally. This group showed, after 48 hours, a moderate uveal reaction: +2 aqueous beam, an occasional stringy exudate attached to the pupil, and a powdery deposit on the capsule. On the basis of clinical appearance alone there was no appreciable difference between the different strains of bacilli (Figs. 11, 12, and 13). CxRP tests done on the same day showed only one positive serum response,

Fig. 10.—Unusual edematous reaction in an otherwise quiet eye following intravitreal injection of tuberculin P. P. D. Disc is edematous, and the choroid is detached by an albuminous fluid. Large amounts of the same fluid are found in the anterior chamber. Cellular infiltration is minimal.

TABLE 10.—*CxRP Reaction to Tuberculin P. P. D.**

Rabbit No.	Tuberculin P. P. D., Mg./Cc.	CxRP Reaction to Tuberculin P. P. D.					
		Before Injection, Blood Serum	1.0 Cc. P. P. D., I. V., Blood Serum	0.1 Cc. P. P. D., Intravitreally, 1 Mo. Later		0.1 Cc. P. P. D., Intracamerally, 2 Wk. After Intravitreal Injection	
				Blood Serum	Primary Aq., O. D.	Blood Serum	Primary Aq., O. D.
300	0.05	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.
301		Neg.	Neg.	Neg.	Neg.	Neg.	Neg.
302		Neg.	Neg.	Neg.	Neg.	Neg.	Neg.
303	0.002	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.
304		Neg.	Neg.	Neg.	Neg.	Neg.	Neg.
305		Neg.	Neg.	8+	Neg.	Animal died	

* This Table shows that P. P. D. is ineffectual in producing a positive CxRP reaction. Note in Rabbit 305 the prognostic value of a strong positive CxRP reaction in the blood serum, indicative of overwhelming systemic response.

Fig. 11 (Rabbit 311).—Primary tuberculous infection by intravitreal injection of Strain JH4. Section shows vitreous inflammatory reaction with destruction of retina.

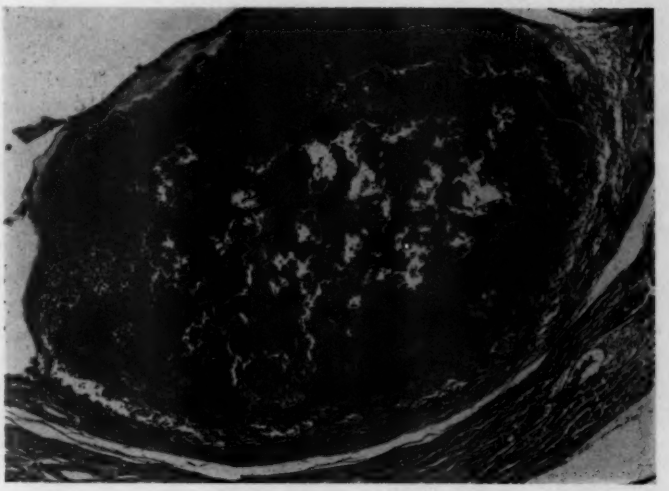

Fig. 12 (Rabbit 312).—Primary tuberculous infection following intravitreal injection of Strain JH16. This section shows a typical tuberculous caseating vitreous abscess with destruction of contiguous retina.

Fig. 13 (Rabbit 314).—Primary tuberculous infection following intravitreal injection of Strain BCG. Ciliary body, showing tuberculous infiltration which spreads from contiguous vitreous infection, as shown in Figure 12. Compare Figures 12 and 13 with mild and more localized reaction in the immune animal (Fig. 14).

TABLE 11.—*CxRP Reaction to Intravitreal Injection of Avirulent Strains of Tubercle Bacilli into Uninfected Rabbits*

Rabbit No.	Strain	CxRP Reaction to Intravitreal Avirulent Tubercle Bacilli				
		Before Injection, Blood Serum	4 Days After Injection		1 Mo. After Injection	
			Blood Serum	Primary Aq., O. D.	Blood Serum	Primary Aq., O. D.
311	JH4	Neg.	Neg.	1+	Neg.	Neg.
312	JH16	Neg.	Neg.	2+	Neg.	Neg.
313	JH6	Neg.	2+	5+	5+	1+
314	BCG	Neg.	Neg.	2+	Neg.	Neg.
315	H37RA	Neg.	Neg.	1+	±	1+

Fig. 14 (Rabbit 336).—Secondary tuberculous infection by intravitreal injection of Strain JH4. Section showing prepapillary and deep vitreous reaction. Vitreous bands extend from disc anteriorly to ciliary body. Compare the mild reaction of this immune animal to the severe uveitis (Fig. 11) in a nonimmune animal.

TABLE 12.—*CxRP Reaction to Intravitreal Injection of Avirulent Strains of Tubercle Bacilli into Previously Infected Rabbits*

Rabbit No.	Strain	CxRP Reaction to Intravitreal Avirulent Tubercle Bacilli		
		Before Injection, Blood Serum	After Injection	
			Blood Serum	Primary Aq., O. D.
336	JH4	Neg.	3+	3+
334	JH16	Neg.	Neg.	Neg.
350	JH6	Neg.	Neg.	2+
335	BCG	Neg.	Neg.	Neg.
338	H37RA	Neg.	Neg.	1+

but all aqueous samplings were positive. It is interesting to note that the only rabbit with positive CxRP in the blood serum (Strain JH6) also showed the strongest aqueous reaction. One month later the tests were repeated. The rabbit infected with JH6 strain was still the only one with a strongly positive serum. From the aqueous samplings only two remained weakly positive (Table 11). The globes were white; anterior chambers were extremely shallow, precluding any further sampling; the irises showed various degrees of atrophy; there were an occasional nodule resembling a Koeppe nodule and a dense grayish pupillary reflex resulting from an organized vitreous.

3. The last part of this study was concerned with tuberculous uveitis in a previously sensitized animal. Five rabbits each received an intravenous injection of one of the above-mentioned avirulent strains of tubercle bacilli. One month later 0.1 cc. of the same strain was injected intravitreally.[12]

At the end of three days one could observe a moderate uveal activity in three eyes, consisting of a flare, a few minute dot-like deposits on the capsule, and a variable number of occasional cells (Fig. 14). Those three eyes showed a positive CxRP reaction in the aqueous, its intensity being closely related to the clinical picture. Only one rabbit exhibiting a +3 CxRP reaction in the aqueous presented a positive blood serum reaction (Table 12).

The following conclusions may be drawn from this part of the studies.

1. Tuberculin purified protein derivative appears to be a poor stimulus for localized or systemic CxRP production. A previously sensitized animal showed also a weak local and systemic response, regardless of the route of introduction of the shocking dose (vitreous or anterior chamber). The only strongly positive blood serum reaction belonged to a rabbit which became very ill toward the end of the experiment and died shortly after the anterior chamber was tapped.

2. By contrast, live tubercle bacilli produced a uniformly positive CxRP reaction in all the infected eyes. Here, a close rela-

tionship between the clinical picture and the intensity of the reaction could be detected. At the end of the month, when the uveitis was subsiding, the CxRP titer correspondingly declined.

3. An animal sensitized by previous injection of tubercle bacilli will respond to an intravitreal reinfection with variable results, from intense reaction to none. Here, again, the CxRP titer was highest in the highly reactivated eye and nil in the quiescent eye. It appears as if the reinfection type of uveitis is more erratic in its course, but, regardless of the mode of production, the CxRP titer reflects the intensity of the inflammation and not the state of sensitivity to tubercle bacillus.

Comment

The question of transfer of CxRP through the rabbit blood-aqueous barrier can be answered affirmatively on the strength of the first experiments. The ratio of CxRP titer in the secondary aqueous to the CxRP titer in blood serum of the same animal is, we surmise, the same as for the other protein fractions not present in the normal aqueous. This statement, however, needs further confirmation through controlled microanalytic methods.

The second series of experiments demonstrated that Cx-reactive protein is produced within the rabbit globe in response to an intraocular stimulus. Under experimental conditions this reaction can remain confined to the eye, the blood serum not participating in the CxRP appearance.

The purpose of Experiments 3, 4, 5, and 6 was to explore the possibilities of CxRP test in experimental uveitis in rabbits. The conclusions drawn from this part of our studies are of necessity presumptive. Statistical evaluation would be misleading, because the number of rabbits assigned to each phase was not large enough to lend itself to mathematical presentations.

Uveitis produced with horse serum in a new animal has no CxRP-stimulating value. Anaphylactic shock produced with the same horse serum intravenously will give a uniformly positive serological response; however, an anaphylactic state produced by an intravitreal injection is less effective. Uveitis produced in a sensitized animal will give a fairly uniform positive aqueous reaction. Our impression is that the degree of positivity depends on the intensity of the inflammation.

Herpes simplex virus and the pyogenic bacteria (M. pyogenes var. aureus and S. pyogenes) are all capable of stimulating the appearance of CxRP within the globe. In our experiments there also appeared, almost simultaneously, a systemic reaction. The assumption that the organisms rapidly reach the general circulation appears the most plausible. Since in human bacterial uveitis the systemic invasion is rather the exception than the rule, one can surmise that the rabbit's eye is proportionally a larger part of the entire organism than the human eye, and therefore is capable of inducing more of a generalized reaction. Perhaps, also, the ocular vascular system in the rabbit is less insulated from the general circulation than that of the human eye. Here, again, we should like to draw attention to the remarkable barrier formed by the iris-lens-ciliary body in keeping the aqueous free from the intravitreally inoculated infecting agent in spite of the severity of the inflammation.[8]

The opinion expressed in the literature that bacterial growth inhibits the appearance of C-reactive protein can be, with some limitations, applied to Cx-reactive protein. It is possible that living organisms in the aqueous actually inhibit the formation of CxRP or through chemical or immunological affinity prevent its detection.

Tuberculin purified protein derivative has very little ability to stimulate production of CxRP, locally or systemically. This applies to new as well as to sensitized animals. Live tubercle bacilli, however, appear to have a strong local antigenicity in intact animals and, unlike the pyogenic and viral agents, remained, with one exception, local-

ized. This self-limited tendency as compared with the rapid systemic spread of the herpes simplex virus, Streptococcus, and Micrococcus is interesting. The systemically infected rabbits showed an irregular blood and aqueous response. Curiously enough, human blood sera of patients with active tuberculosis were positive in only 10% of cases, according to Glaskin et al.[2] The lower antigenicity of tubercle bacillus in a sensitized animal is also of great interest, although not clearly understood. If one compares the over-all clinical picture of tuberculous uveitis with the CxRP results, one is tempted to conclude that the CxRP reaction reflects primarily the intensity of the intraocular inflammation. Primary tuberculous uveitis exhibited a uniformly intense reaction and a uniform CxRP response. In a systemically infected animal the intraocular tuberculous process is spotty, and the CxRP response reflects this irregular pattern fairly well.

Summary and Conclusions

Pertinent data concerning C- and Cx-reactive protein (CRP and CxRP) and antibody levels in the aqueous are briefly reviewed. On the basis of these data, the scope of this study is outlined as follows: (1) to demonstrate the passive transfer of CxRP through the blood-aqueous barrier, (2) to demonstrate the active intraocular production of CxRP, and (3) to study the relationship between aqueous CxRP level and experimental uveitis.

The ensuing animal experiments proved conclusively the passive transfer of CxRP across the altered blood aqueous barrier, the blood aqueous level ratio being still under investigation.

These experiments leave very little doubt that CxRP can be produced within the globe in experimental uveitis. Its selective appearance is not yet fully defined. A single intraocular horse serum infection will show very little response. An animal highly sensitized to horse serum acquires a positive systemic reaction, and its intraocular tissues will respond promptly to an intraocular injection.

Intravitreal inoculations of herpes simplex, Streptococcus pyogenes, and Micrococcus pyogenes var. aureus (Staphylococcus aureus) have a uniform stimulating effect on CxRP appearance in the aqueous. Their rapid systemic spread follows, with a strong systemic response. The presence of living organisms in the aqueous appears to have an inhibitory effect on CxRP detection.

Intravitreal injection of tuberculin purified protein derivative shows no CxRP-stimulating ability in a new or sensitized animal. By contrast, intravitreal injection of live tubercle bacilli gives a strongly positive aqueous reaction. Compared with herpes simplex virus, the Streptococcus, or Micrococcus, the tubercle bacillus shows little tendency to systemic invasion. Previously infected animals undergoing an intraocular reinfection show a variable systemic and intraocular response closely related to the clinical course of the disease.

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Studies of the Crystalline Lens in Humans Receiving Galactose over Prolonged Periods

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A. Introduction

Since the production of cataract was first observed by Mitchell and Dodge (1935) and by Yudkin and Arnold (1935) following the feeding of rats with a diet rich in lactose, many investigators, including Day, Bellows, Roaner, Jess, Cook, Susaki, Cashell, and Kon, have confirmed its occurrence in animals with both galactose and lactose. Lens changes occur more rapidly with galactose than with lactose, and the changes follow a rather predictable pattern. The earliest changes are vacuoles in the periphery and in the anterior cortex, while a posterior polar opacity and a nuclear opacity may precede complete maturation. The actual growing fibers are affected first, the cortex in adult animals and whole lens in the young. In rats mature cataracts are usually present by the 30th day.

B. Procedure

Observations were made on 12 patients who received galactose daily for periods of 2 to 12 months.

The observations included slit-lamp examinations periodically as well as opthalmoscopic examinations under full dilatation.

Eight patients received 100 gm. of galactose daily for four months (50 gm. intravenously and 50 gm. by mouth); one received 10 gm. daily subcutaneously for three months, and three received 25 gm. daily intravenously (50 cc. of 50% solution) for two months.

The galactose administrations are continuing, and a further report will be made at a later date.

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C. Conclusion

Thus far, none of the patients has shown any evidence of cataract formation.

This report is submitted because of the dearth of such studies in humans.

It might parenthetically be stated that I did not specifically administer galactose to humans to see if I could cause cataracts; this is merely the by product of another experiment, which justified and warranted the administration of galactose to humans.

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Surgery of Developmental Cataract

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The purpose of this paper is to present a technique for the surgery of developmental cataract which is simple, safe, and surgically sound. The paucity of articles on this subject in the medical literature is surprising.

Since the term congenital merely implies a point in time, it is best to term these cataracts developmental. As Regnier [1] points out, cataracts in babies, whether present at birth or formed during infancy, should be called developmental rather than congenital, because the development of the lens in the human eye proceeds steadily, without any particular change in progress at the time of birth.

The wide variety of lenticular involvement, from tiny spots to complete opacification, is well known. Of primary importance in the visual prognosis, whether surgery is performed or not, is the frequent presence of associated ocular defects. Among these are amblyopia, nystagmus, strabismus, microphalmos, atrophy of the iris, intolerance to atropine, poor pupillary dilation, shallow anterior chamber, pigmentary changes in the fundus, optic atrophy, congenital glaucoma, corneal opacities, corneal edema, anisocoria, iris coloboma, persistent pupillary membrane, heterochromia iridis, subluxation of the lens, lenticonus, and oblique palpebral fissures.

There frequently are serious associated nonocular defects. These include deafmutism, cardiac anomalies, failure to thrive, mental retardation, and microcephaly.

Gregg [2] was the first to observe the relation of maternal rubella to cataracts and other anomalies. He [3] stated that these are dense white cataracts which completely fill the undilated pupil. The opacity is surrounded by a smoky zone which is much less dense. In the periphery there is a thin clear zone through which a fundus reflex can be obtained. It appears that other infections in pregnancy may give rise to similar embryopathy. Among these are mumps, varicella, poliomyelitis, and infectious hepatitis. Perhaps there are a host of other virus illnesses which pass unnoticed. The time of infection is most important. The lens is most likely to be involved if the mother is infected before the eighth week. After the 12th week the lens is likely to escape unscathed. François and Verriest [4] state that impairment of hearing is more likely around the end of the third month, whereas cataract formation occurs at the end of the second month.

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Choice of Operation

The choice of operation and its evolution brings us to the purpose of this report. A form of needling has been the most favored technique in the surgical management of developmental cataract. It is probably still the most frequently performed operation. The trend, however, is decidedly toward abandonment of discission in favor of linear extraction. The latter technique must offer tremendous advantages to make a surgeon give up a surgical procedure such as discission, which is technically one of the simplest intraocular operations practiced.

In spite of the trend, Kirby [5] would not consider a linear extraction in the first year of life. Clark [6] performs needling up to the age of 12 years and linear extraction at from 12 to 25 years. Meller [7] also used linear extraction only after the 12th year. Arruga [8] stated that the operation of choice is discission in young children. This list could be extended ad infinitum. However, it is unfair to quote surgeons' preferences,

since, in light of present progress, these preferences might differ today.

Discission.—What happened to the simple discission? The answer must be in the complications which follow this seemingly benign operation. The disadvantages of this technique will be considered.

1. Multiplicity of Operations: Cordes [9] stated that this constituted a real disadvantage from the parents' point of view. To this, let it be added that the disadvantage is far greater from the infants' point of view, since, as Falls [10] pointed out, they are often poor anesthetic risks (possibly owing to liver damage).

2. Frequent Failure to Obtain an Adequate Pupillary Opening: Von Graefe's dictum was, never needle in the face of a small pupil. This can result in pupillary block with resultant iris bombé. An inflammatory membrane frequently occludes the pupil.

3. Disturbance of Vitreous: Multiple needlings invariably disturb the vitreous. This may cause glaucoma due to blockage of the pupil by vitreous and may cause vitreous in the anterior chamber. This may also cause corneal edema and bullous keratopathy due to vitreous contact with the cornea. Chandler [11] pointed out that this was the commonest cause of glaucoma in developmental cataract surgery and the most disastrous. It has also been recognized that late retinal detachment occurs in a horrifying number of persons operated on for developmental cataract. After Ziegler through-and-through needlings, Shapland [12] reported 33 retinal detachments out of 40 cases, after an average of 24 years. Moore [13] stated that detachment was most frequent after needlings and occurred here in 7% of cases. Cordes,[14] in a Jackson Memorial lecture, beautifully demonstrated with pathological specimens that detachment was less likely after linear extraction.

Why does detachment of the retina occur? Many reasons have been given, such as delayed resorption of lens material with recurrent irritation of the uvea. However, the consensus appears to follow Chandler's [11] feeling that the more the vitreous is disturbed, as with repeated operations, the greater is the danger of detachment.

4. Frequency of Glaucoma: Vitreous block has already been mentioned. Rapid swelling of the lens after discission, especially with too small a capsule opening, cortex in the anterior chamber blocking the angle, and the above-mentioned iris bombé are other causes.

Linear Extraction.—Since linear extraction is more likely to accomplish its goal in one operation, the risk of anesthesia and the risk of vitreous disturbance with subsequent glaucoma and retinal detachment are lessened.

Surgical Indications

Surgery should be done for bilateral complete cataracts either present at birth or developing during the first few months of life; also, when there is severe involvement of both eyes without complete opacification of the lenses, as in large and very dense zonular cataracts. If the involvement of one lens is severe and that of the other lens is mild (vision 20/50 or better), surgery should not be done. These are Chandler's [11] criteria, and Cordes [9] concurs.

Because of the high frequency of serious complications, Costenbader, in a personal communication to us, pleaded conservatism in the management of these cataracts. He preferred to retain the lens, using optical iridectomy or chemical dilation of the pupil.

Age for Surgery

There is a great diversity of opinion regarding the proper age for surgery. It appears that most surgeons consider early surgery (within the first year) advantageous when the opacification is complete or almost complete. Certainly, general development is more rapid if vision is improved. However, the impossibility of preventing restlessness in infants frightens most surgeons. Statistics which show that the later the surgery the superior the results are

entirely misleading. Cases done earlier are usually the worst cases. These are usually associated with other ocular defects which preclude good vision. Also, as to difficulty of management, it is our opinion that it is easier to manage a child aged 6 to 18 months than a 2- to 3-year-old.

Falls [10,15] operates on one eye at the age of 6 months if complete bilateral cataracts are present; otherwise, he waits until 2½ years. Cordes [9] operates on the first eye at the age of 6 months in the hope that, by establishing fixation, nystagmus may be prevented. He then operates on the second eye somewhere in the 3d year. Kirby [5] felt that the nystagmus was due to a defect in central vision and that early surgery could not help this. Horay [16] stated that his results were equally satisfactory when done in the first year or after. Gregg [3] indicated that early interference was not only justified but necessary because of the danger of nystagmus. Regnier [1] would wait at least two and one-half years. The difference of opinion is great, but we wonder how much of this is due to fear of difficult postoperative management in infancy instead of purely ocular factors.

Visual Prognosis

Visual prognosis must be guarded, especially if there are associated anomalies. Regnier [1] stated that 60% achieve 20/70 or better vision if no other ocular defect is present. Only 10% achieve this otherwise. Falls [10] observed that of 29 cases who had a discission and linear extraction, 55% achieved vision of 20/40 or better but only 27% of 94 cases having discissions alone achieved this level of vision. However, it may have been that discissions were done on the youngest (more severely involved) cases. In Falls' series 53% achieved vision of 20/100 or better; 17% were blind. Vision of Jaeger 4 to 7 or better was achieved in only 17%. No patient with nystagmus achieved better than 20/50 vision. Owens and Hughes [17] reported vision of 20/70 or better in only 11% of patients with associated ocular defects and in 62.4% without defects. There were associated ocular defects in 56% of their series.

These figures are listed merely to show that visual prognosis must be guarded. The success of surgery cannot be measured by visual achievement, since a perfectly well performed operation may not provide good vision at all, owing to other defects. In evaluating surgical techniques the criteria for successful surgery must rest with other factors, such as adequate pupillary opening and an undisturbed vitreous.

Comment on Linear Extraction

Vitreous loss can certainly occur with linear extraction. Owens and Hughes [17] report vitreous loss in 16.1% of cases, and Bagley,[18] in 10%. Chandler [11] states that vitreous loss here is a catastrophe and not infrequently results in ultimate loss of the eye.

It is believed that the current trend toward operating on a softer eye, with use of digital pressure, as first advocated by Chandler in senile cataract surgery, will significantly lessen the incidence of vitreous loss.

Faulty technique is probably the most important cause of vitreous loss. The toothed capsule forceps should be used only once. If the surgeon feels that too small a bite was made, he must not make a second attempt. The position of the posterior capsule moves anteriorly after a capsulotomy. A

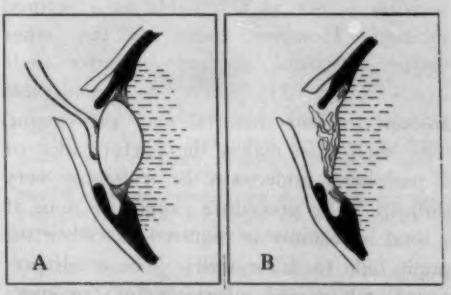

Fig. 1.—Note the position of the hyaloid in *A*. The toothed capsule forceps engages the lens capsule. No second attempt to grasp the capsule should be made, because the hyaloid moves anteriorly and can be grasped with the forceps.

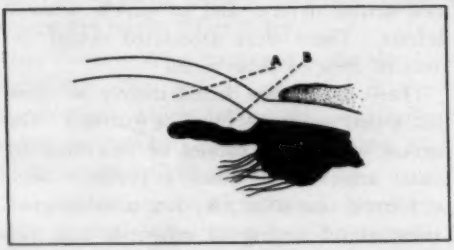

Fig. 2.—*A* represents the beveled incision in the cornea. Note the position of penetration of the posterior portion of the cornea. This leaves a large shelf where lens remnants can accumulate. The lens nucleus may be trapped here. The performance of an iridotomy is difficult. *B* represents the limbal incision in our technique.

second grasp will likely penetrate the hyaloid (Fig. 1). Another lapse of technique is the compulsion on the part of the surgeon to do too much. Chandler [11] stated that "the mark of the skillful linear extraction surgeon is said to be the ability to know when to quit."

The Cordes [9] modification of the Barkan linear extraction is so well known that it will not be described in detail here. However, the points which we feel are weak will be discussed.

The incision is made with a keratome, starting 1.5 to 2.0 mm. below the upper limbus. The keratome lies parallel to the plane of the iris, so that the tip enters the anterior chamber approximately 3.0 mm. or more below the limbus. This creates a valve-like incision which should seal off the anterior chamber. It is felt that such an incision is not as acceptable as a sutured incision. However, there are two other major criticisms. A large superior shelf exists (Fig. 2), where a considerable amount of lens material may get caught. The shelf also makes the performance of a peripheral iridectomy or iridotomy very difficult. The procedure cannot be done if a total iridectomy is required (as when the pupil fails to dilate well). The small prepared stab wound inferiorly for the injection of air requires further manipulation, which may be complicated. It is thought that the main advantage of the valve-like incision over the sutured limbal incision is that a second anesthetization was not required for suture removal. With the advent of absorbable surgical (gut) sutures, suture removal is no longer necessary. An incision at the upper limbus makes the operation easier.

The ideal operation must satisfy the following criteria: It must (1) be a single procedure, (2) provide an adequate pupillary opening, (3) keep the iris free of the wound, (4) keep the hyaloid intact, and (5) not result in glaucoma.

In view of some of the large series of cases reported, we are hesitant to report our technique on a small number of operations. However, since the theoretical advantages were borne out in every case, this report appeared warranted.

The surgical indications are those originally outlined by Chandler.[11] In the case of total or almost total bilateral cataracts, the first eye can be operated on at the age of 6 months.

Technique Presently Advocated

Seventy-five minutes before surgery, a solution of homatropine, 1 drop every two minutes for four doses, is placed in the eye to be operated on. This is followed immediately with a 10% solution of phenylephrine (Neo-Synephrine), 1 drop in the same eye every two minutes for four doses.

General anesthesia, with use of an endotracheal tube, is employed. Lid akinesia is performed, with use of a lidocaine (Xylocaine), hyaluronidase (Alidase), and epinephrine mixture. A retrobulbar injection of 1 cc. of this mixture is performed. No canthotomy is used. Lid sutures are placed. A superior rectus bridle suture is placed. If the pupil is not satisfactorily dilated, 2 drops of epinephrine (1:1000) are injected subconjunctivally toward the superior limbus. Pressure is then exerted over the closed lids for three minutes, with use of two fluffed-out 4×4 in. gauze pads. Pressure is let up every 30 seconds for 3 seconds.

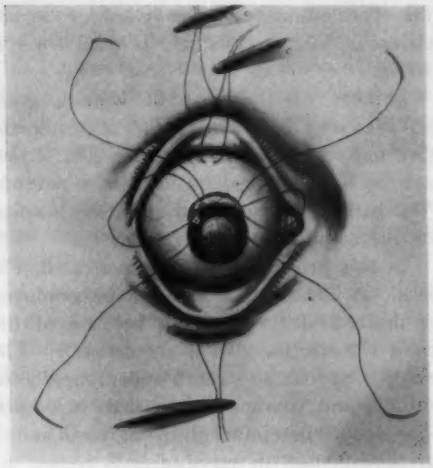

Figure 3.—A small peritomy has been performed. Two preplaced 000000 chromic gut sutures are placed in grooves. Two additional postplaced sutures will be inserted between the two shown in the drawing.

The conjunctiva at the upper limbus is dissected from the cornea and allowed to retract slightly so that the limbus is bared for approximately 8 mm. Two grooves in the limbus are fashioned at 11 o'clock and 1 o'clock. A 000000 chromic gut suture with a sharp needle (Ethicon No. 790) is employed in each groove. A loop of suture is withdrawn from the groove (Fig. 3).

A keratome incision is made at the limbus between the grooves. The incision is enlarged in both directions while the assistant spreads the suture arms, thus exposing the grooves. The entire incision should measure 6 to 8 mm. This is slightly less than one-quarter of the circumference of the cornea.

A small peripheral iridotomy is performed at 12 o'clock. The iris is easily grasped and drawn out of the wound. A cut close to its root is made with de Wecker or Barraquer scissors. If the pupil is not fully dilated, a complete iridectomy is performed.

At this point, two additional corneoscleral sutures are placed between the two previously placed sutures. This is a small space for two sutures, but they are necessary in order to obtain an air-tight closure of the wound. The sutures are drawn from the

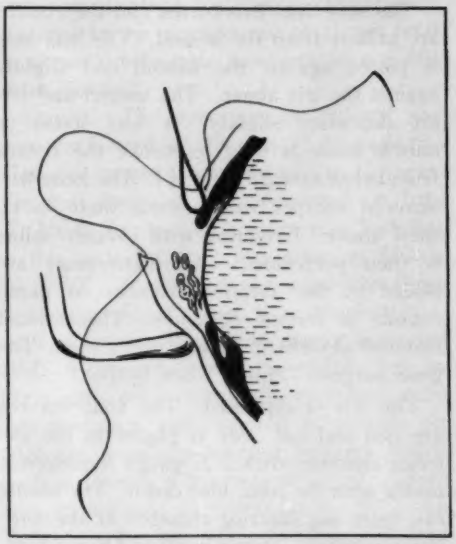

Fig. 4.—Lens remnants are gently stroked after the capsulectomy. Slight pressure is made with a wire loop superiorly against the sclera and iris. The lens nucleus must be milked out in this fashion.

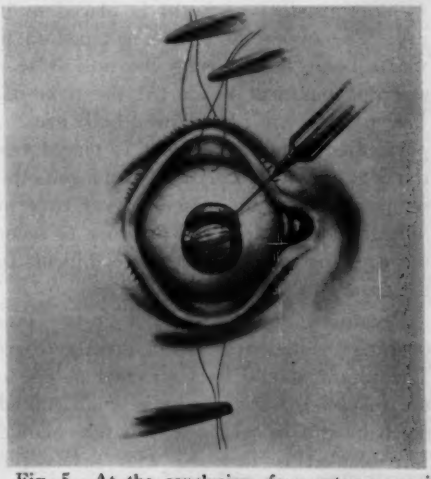

Fig. 5.—At the conclusion, four sutures are in place. A filed-down 27-gauge needle is used to place a bubble of air in the anterior chamber. The needle is placed between the most temporal suture and the temporal extremity of the incision. No separate groove for air is required.

wound, leaving adequate loops. The toothed forceps (Schweigger or Fuchs) enters the anterior chamber at 12 o'clock. The lips are spread wide, and the capsulectomy is performed. Only one attempt is made.

The soft clear lens cortex and the nucleus are milked from the wound. The lens loop is placed against the wound and slightly against the iris above. The wound and iris are depressed slightly. A lens spoon or muscle hook is used to stroke the cornea from below upward (Fig. 4). The loose lens material escapes easily, since there is no shelf above. Irrigation with isotonic saline is then performed. No instruments are placed in the anterior chamber to grasp capsule or cortical remnants. The residual material absorbs in almost every case. The good surgeon "knows when to quit."

The iris is reposited. The four sutures are tied and cut. Air is placed in the anterior chamber with a 27-gauge hypodermic needle with the point filed down. The needle can enter the anterior chamber at the temporal extremity of the incision (Fig. 5).

A subconjunctival injection of 50,000 units of aqueous penicillin (in 0.5 cc. of saline) is made inferiorly. Chloramphenicol (Chloromycetin) ointment is placed in the eye. The upper lid suture is taped to the malar bone, thus closing the lids. Use of atropine ointment is started the next day. Eye patches are placed over both eyes. A perforated aluminum shield is placed over the operated-on eye. A 2 in. bandage is then wrapped around the patient's head, covering only the operated-on eye in order to secure the dressing and make it more difficult for the infant to remove.

Because of the tight wound closure, postoperative restlessness is not greatly feared. The infant should be restrained in one of the following ways. If he is small enough, the baby can be wrapped in a thin blanket. The blanket is fastened with safety pins so that the hands cannot be brought out. For larger children, wrist restraints fastened to the sides of the crib can be used. Elbow splints are routinely used. These children are not overly restless because the eyes are covered, since there was practically no vision to begin with.

The dressings are changed on the following day. Atropine ointment is placed in the operated-on eye. The fellow eye is uncovered. The metal shield is used for one week.

Because of the air-tight wound, great liberties may be taken as far as postoperative movements are concerned. The infant can be held and fed by nurses or parents. The patient is discharged from the hospital on the second postoperative day.

In this procedure no conjunctival flap is used. A limbal-based flap may be employed if desired. It is felt that, because of the tight closure, the flap is unnecessary. The sutures appear to absorb more rapidly in infants and young children than in adults. The danger of epithelial downgrowth is not great with use of gut sutures.[10]

Comment

What are the principal points which make this procedure a satisfactory one?

1. The incision occupies only one-quarter or less of the circumference of the limbus.

2. The incision is air-tight. It should be practically impossible to fit an anterior chamber irrigator tip or an iris spatula between any two sutures. Only a 27-gauge needle can be used to place air in the anterior chamber.

3. There is practically no shelf superiorly where loose capsule fragments or cortex can lodge. This makes the delivery of the bulk of lens material much easier.

4. Air in the anterior chamber through the limbal incision is used to separate iris and residual lens material from the wound. A separate stab wound for air is not required.

5. Sutures are absorbable. The advantage of this is obvious.

6. The globe is softened digitally. This lessens the chance of vitreous loss.

Complications.—How can this procedure lessen the chances of the usual complications of linear extraction as outlined by Cordes?[9]

1. Delayed Restoration of the Anterior Chamber: This may occur in the Barkan-Cordes technique if the incision is not valve-like enough. It is less likely in a perfectly

air-tight incision, which is provided by four sutures in a 6 to 8 mm. incision.

2. Anterior Synechiae with Pupil Drawn Up: It is easier to obtain an incarceration in the valve-like incision, since it is intracorneal and closer to the probable position of the iris sphincter.

3. Occlusion of the Pupil: No matter what procedure is used, the pupil must be kept dilated for a long time.

4. Membrane Formation: This is due to iritis associated with an inadequate opening in the capsule or inadequate pupillary dilation. Adequate use of postoperative mydriatics is necessary.

5. Loss of Vitreous: Softening of the eye by use of three minutes of digital pressure via two fluffed-out 4×4 in. gauze pads is the best prophylaxis against vitreous loss. Also, a limbal incision makes it easier to express the lens fragments than is the case with a 3 mm. corneal shelf as in the Barkan-Cordes procedure. Thus, less manipulation is required in the anterior chamber, and this lessens the chances of vitreous loss. Of course, the answer is to know "when to quit." Small lens remnants should not be pursued, since they will undoubtedly absorb.

6. Glaucoma: Chandler [11] considers vitreous block of the pupil and vitreous in the anterior chamber as the most serious cause of glaucoma. Thus, the hyaloid should remain undisturbed, as discussed above. Iris incarceration can be prevented by using air in the anterior chamber and postoperative mydriasis. As mentioned above, the limbal location of the incision is safer, in our opinion. Glaucoma is not as common as in discission.

7. Detachment of the Retina: The consensus favors the view that a ruptured hyaloid is a possible precursor of retinal detachment. An intact hyaloid should be maintained in almost every linear extraction, whereas this is almost impossible in multiple discissions.

It is strongly felt that this technique, if carefully performed, will result in a minimum of serious complications. Conservatism (optical iridectomy or pupillary dilation) in the management of almost total or dense rubella-type cataracts is not felt to be justified.

Results.—The operation as outlined has been performed on 17 eyes of 10 patients. The ages ranged from 6 months to 13 years. The first operation was performed on July 17, 1954. In the most recent case included in this series surgery was done on March 26, 1957. Because of the relatively short follow-up period, very late complications, such as retinal detachment, cannot be evaluated. However, it can be stated that in every case, without a single exception, only one operation was required to provide an adequate pupillary opening through which a clear fundus reflex was obtained. There was no instance of vitreous loss. In every instance a fundus reflex could be obtained during the first few postoperative days. It can be assumed that postoperative glaucoma presented no problem, since recovery was uneventful in every case. The eyes become white remarkably early in the postoperative course. The bulbar injection is far less than that seen after senile cataract surgery.

In both eyes of two patients it was necessary to perform a complete iridectomy because of inadequate pupillary dilation. There was not a single instance of iris prolapse, iris incarceration, or drawn-up pupil. Postoperative iritis was not encountered in the older children, but the majority of the patients could not be adequately examined for this because of their young ages.

There was no instance of postoperative hyphema, delayed formation or secondary loss of the anterior chamber, seclusion, or occlusion of the pupil.

The remarkably benign postoperative courses encountered represented the major factor in prompting this report, in spite of the small number of cases.

Report of Cases

Case 1.—A boy had mild cerebral palsy, athetoid type, with nystagmus. There were bilateral dense rubella-type cataracts. Hear-

ing was unimpaired. There was no mental deficiency and no cardiac pathology. A linear extraction was performed on the left eye at the age of 3 years. The left eye underwent the same procedure two months later. Recovery was uneventful in both cases.

CASE 2.—A girl had almost total bilateral cataracts and no associated ocular or systemic defects. A linear extraction was performed on the left eye at the age of 8 months. The identical procedure was performed on the right eye at the age of 14 months. Recovery was uneventful in both cases.

CASE 3.—A girl was noted to have bilateral zonular cataracts. Visual disturbance was first reported at the age of 7 years. The vision suddenly became much worse at the age of 12 years. There were no associated ocular or systemic defects. The patient was first examined at the age of 10 years. At the age of 12 years 3 months the cataract in the right eye was mature and vision in the left eye was reduced to finger counting at 6 ft. A right linear extraction was done on the right eye, and nine months later the same procedure was done on the left eye. Recovery was uneventful. This child's vision is correctible to 20/20 and J 1 in both eyes.

CASE 4.—A Negro boy with cerebral palsy (spastic quadriplegia) and probable mental deficiency was first examined at the age of 6 months. There were bilateral very dense rubella-type cataracts. There was an alternating esotropia with searching movements in each eye. At the age of 8 months an uneventful left linear extraction was performed. Recovery was normal. Surgery on the second eye has been delayed because of the death of the mother.

CASE 5.—A boy was first examined at the age of 6 months. There were bilateral dense rubella-type cataracts. There was no significant prenatal history. A diagnosis of an interventricular septal cardiac defect was made. No accurate estimate of hearing or of mental capacity has been made, although development appears normal within the limits of a "blind" infant. There were bilateral searching ocular movements. The right globe was normal in size, but the left eye was possibly microphthalmic. At the age of 7 months an uneventful right linear extraction was performed. After the passage of the endotracheal tube, the infant became apneic. The anesthesiologist felt that it was a reflex apnea. It lasted over 40 minutes, respiration being maintained by the anesthesia bag. The heart sounds were good except for the murmurs. Surgery was performed after the respirations became spontaneous. The recovery was uneventful. The second eye will be operated on when the patient is one year old.

CASE 6.—A girl was first examined at the age of three years. There was an almost total cataract in the left eye and a dense zonular cataract in the right eye. There were no associated ocular or systemic defects. At the age of 3 years 1 month an uneventful left linear extraction was performed. Four months later the identical procedure was performed on the left eye. Recovery was uneventful. This child wears her aphakic lenses easily, and vision appears to be adequate.

CASE 7.—A boy with cerebral palsy (athetoid) was first examined at the age of 15 months. There were bilateral dense rubella-type cataracts. There were no other systemic defects except for the cerebral palsy. There was nystagmus on gaze to the right. At the age of 16 months an uneventful left linear extraction was performed. Six weeks later the same procedure was performed on the right eye. Recovery was uneventful in both eyes. In both cases a full iridectomy was required, owing to insufficient pupillary dilation.

CASE 8.—A Negro boy was first examined at the age of 2 years. There were bilateral almost total cataracts. There was no nystagmus. A cardiac murmur was present, but it was felt to be of probable functional origin. There were no other defects. At the age of 2 years 2 months an uneventful right linear

extraction was performed. This was done on the left eye three months later. Recovery was uneventful. The patient does not yet tolerate aphakic lenses.

CASE 9.—A girl was first examined at the age of 7 years. Four needlings had been performed on the right eye. The pupil was very small and bound down. No fundus reflex could be obtained. With an aphakic lens, vision was finger counting at 8 ft. The left eye had a dense zonular cataract with vision of finger counting at 4 ft. The patient had a cleft palate, several large (double) teeth, and two fused toes. An uneventful left linear extraction was performed. Aphakic lenses were prescribed 10 weeks later. Vision was corrected to 20/50−3. Further surgery will probably be done on the right eye.

CASE 10.—A boy was first examined at the age of 22 months. The child had cerebral palsy (spastic hemiplegia). There appeared to be no mental deficiency. There were bilateral almost total cataracts. There was bilateral nystagmus. At the age of 23 months an uneventful right linear extraction was performed, and at the age of 27 months an uneventful left linear extraction was performed. Recovery was normal in both eyes.

Further Comment

It is realized that surgical techniques change with the times. In spite of the fact that the American ophthalmic literature emphasizes the intracorneal section, Paul Chandler, in a personal communication to us, stated that his procedure is similar to that used by us. His incision is usually not wider than 6 mm., and two corneoscleral sutures are used. In all infants he performs a full iridectomy and inferior iridotomy.

John McLean, in a personal communication to us, also states that his technique is similar, except that he prefers a limbus-based flap. His preference is for limbus incision, which he says has been overshadowed by papers advocating purely corneal incisions.

Frederick Cordes, also in personal communication to us, stated that his experience indicated that many eyes are lost in congenital cataract surgery where the pupil cannot be easily dilated preoperatively and where a full iridectomy has not been done. He urged that this point be stressed. We concur. There should be no hesitation in performing full iridectomy when dilation is insufficient, particularly in the rubella-type cataracts where there is considerable surrounding clear lens material. Cordes also stated that he usually can inject the bubble of air through the operative wound, but not always. In the latter cases, his preformed puncture is convenient.

Derrick Vail, in a personal communication to us, stated that he was not aware of a description of our technique in the literature. All four communications cited urged publication of this paper. We have undertaken this with the full realization that ours is probably not an original technique and that our series of cases is small.

Summary

The current trend toward abandonment of discission of developmental cataracts in favor of linear extraction is defended.

A method of linear extraction is presented. It offers the following features. Incision is made at the limbus. Four 000000 chromic absorbable surgical (gut) incision, are used to close the 6 to 8 mm. incision, thus providing a practically air-tight closure. This allows for the usual postoperative restlessness seen in these children. The ocular tension is lowered before the section by using three minutes of digital pressure on the closed lids. This decreases the possibility of vitreous loss. A small peripheral iridotomy is used. A bubble of air is placed in the anterior chamber through the closed incision by use of a filed-down 27-gauge needle.

The advantages of this procedure over intracorneal methods, such as the Barkan-Cordes technique, are discussed.

No major complications were encountered in using this method on 17 eyes of 10 patients with developmental cataracts.

1451 N. E. Bayshore Dr. (32).

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Growth of Lens Epithelium in Culture

I. Characteristics of Growth

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The study of lens epithelium in tissue culture was started by Daniel B. Kirby in 1926. He observed the differentiation of the epithelium into lens fibers when the anterior one-third of 52-hour-old chick embryo eyes were cultured in vitro.

In 1929 Kirby, Estey, and Tabor found that cultures of chick embryo lens epithelium were more successful in the regular culture media than when the various constituent inorganic salts were increased more than 25% over the normal. They also found an irregular effect of hypertonic media on these cultures, while a 10% to 15% dilution had a marked depressant action on the growth. When they used a slightly more alkaline medium (pH 8.2), they observed a fairly marked depression of the rate of growth in the cultures.

In 1932 Kirby, Estey, and Weiner observed that an increase in the glucose content of the medium produced no real effect on the growth of chick embryo lens epithelium until a concentration of 578 mg. per 100 ml. was reached, above which glucose proved toxic to these cells. There was no effect on the growth when the glucose content of the medium was decreased. Levulose proved toxic only when a 1160 mg. per 100 ml. level was reached in the medium; galactose was toxic at the 333 mg. per 100 ml. level. Acetone and β-hydoxybutyric acid were toxic, the degree increasing with the concentration of these substances.

A study of mammalian lens epithelium in tissue culture was made Ida Mann in 1948. She used mice embryo lenses and observed an increase in the cytoplasm and the movement of the nucleus to one side. Later there was flattening of the cytoplasm and the cell became bluntly pointed at both ends. These, she considers, are signs of differentiation of lens epithelial cells into lens fibers.

In this study chick embryo lens epithelium was used at the beginning, but this was soon replaced by human lens epithelium.

Materials

Chick lenses were obtained from 5- to 7-day-old embryos. Human lenses were usually obtained from the operating room from cataract operations, but a small number was obtained from donor eyes of the eye bank or from eyes of stillborn infants from the obstetrical department.

Although some of the eye bank lenses may have been more than 24 hours old, all other were obtained within a few hours after removal. The epithelium was cultured the same day the lens were obtained. Solutions and nutrient media used were as follows.

1. Tyrode's solution and Glucosol.*

2. Embryonic extract. This is prepared from 7- to 8-day-old chick embryos. Un-

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* Tyrode's solution without sodium bicarbonate.

der sterile conditions the embryos are macerated, mixed with equal parts of Glucosol solution, and later centrifuged. The supernatant fluid is used as the extract.

3. Horse serum and chicken plasma are obtained from Difco Laboratories, Detroit.

4. The supernatant fluid is prepared under sterile conditions by mixing four parts of horse serum, four parts of Tyrode's solution, and two parts of embryonic extract. Fifty thousand units of penicillin is added to every 100 ml. It is stored in a refrigerator.

Culturing Lens Epithelium

All the work is done in a culture room under sterile conditions. Human lenses are obtained from the operating room in Tyrode's solution. They are transferred to a Petri dish, and the capsules are incised and stripped off. Chicken plasma, 0.30 ml., is introduced into a roller tube (Pyrex test tube) which is rotated so that the plasma covers part of its wall. Then a small piece of lens capsule, about 3 mm. in diameter, is cut and laid flat on the plasma-covered wall of the tube. Supernatant fluid (0.40 ml.) is introduced into the tube, and the latter is rotated again so as to bring this fluid in contact with the plasma at the site of the explant. Within two to three minutes a clot is formed which keeps the explant in place. One and five-tenths milliliters of supernatant is added, and the tube is closed with a No. 1 rubber stopper.

The tubes thus prepared are placed in a rotator inside an incubator. The rotation (nine revolutions per hour) provides a slow washing action that promotes an adequate exchange of food materials and waste products between the fluid and the cells. The cultures are kept at a temperature of 37 C.

With chick lenses a similar technique was used except that ruptured whole lenses from 5- to 7-day-old embryos were used as explants.

Observations

Evidence of growth in cultures of chick lens epithelium occurs in about 12 hours, while in human lens epithelium 48 hours is required. Once growth has been established, adult human lens epithelium seems to be more resistant and less easily destroyed than that of the chick embryo. The initial growth of human lens epithelium is very similar to that of other tissues. Although it may grow on the surface of the lens capsule, it more frequently grows from its edge. At first it grows in sheets, but as the culture becomes older there is a tendency for network formation at the advancing border. Later isolated stellate and spindle-

Fig. 1.—Human lens epithelium growing from edge of lens capsule, 72 hours after culturing. Photo taken from roller tube in vitro.

Fig. 2.—Human lens epithelium growing from edge of lens capsule, six days after culturing. Photo taken from roller tube in vitro.

shaped cells are seen scattered about the periphery of the growth. If the culture is maintained without changing the supernatant fluid, human lens epithelium will survive approximately three weeks. The cells will gradually accumulate fat; later, there is loss of cellular pattern. The culture is considered dead when only cellular debris remains. No evidence of differentiation of epithelium into lens fibers was observed in this study.

In initial experiments on chick embryo lens epithelium it was observed that after a few days the explants developed a dark brownish discoloration in the center which gradually spread to the periphery. It was thought that this might be due to contamination of the culture with iris tissue, even though at the time of culturing the lenses were carefully freed from this structure; however, on staining these cultures with Sudan IV it was shown that these discolorations were accumulation of fat.

Cultures suitable for phase-contrast observation and photography have not been successfully grown as yet, and so actual evidence of mitoses of the cells during growth has not been obtained. Although no controlled studies were made, it was repeatedly observed that human lens epithelium grew earlier and quicker in tissue culture if the explant was obtained from a cataractous rather than from a normal lens.

Conclusion

Human lens epithelium grows favorably in roller-tube cultures. Initial growth occurs in approximately 48 hours. Cells survive up to 21 days when the supernatant fluid is not changed.

Department of Ophthalmology, University Hospital (Dr. Leinfelder).

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Growth of Lens Epithelium in Culture

II. Effects of Oxygen Tension

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The work of various investigators indicates that the lens consumes oxygen and that the amount of oxygen consumption differs in different portions of the lens. Ely (1949) has shown that the capsules and nuclei of both bovine and rabbit lenses have a negligible respiration, that the cortex and epithelium are the only parts that respire, with the epithelium probably playing the dominant role in the oxygen uptake. Kinsey and Frohman (1951) from their findings on the distribution of flavoprotein, cytochrome-cytochrome oxidase, and lactate-pyruvate ratios in different portions of the lens have concluded that the epithelium appears to have a strictly aerobic type of metabolism, while the cortex and nucleus seem to have an anaerobic metabolism.

In order to investigate further the role played by the epithelium in the respiration of the lens, the effect of various oxygen tensions on cultures of growing human lens epithelium was studied.

Cultures of lens epithelium were set up in roller tubes, and growth was established during a period of three to four days. When good growth was observed, the cultures were gassed with one of the following gas mixtures:

1. 95% N_2*
2. 5% O_2+90% N_2*
3. 10% O_2+85% N_2*
4. 95% air*
5. 100% air
6. 50% O_2+45% N_2*
7. 75% O_2+20% N_2*
8. 95% O_2*

Mixtures 1, 4, and 8 were obtained already mixed in gas tanks. Except for air, the gases were mixed in a spirometer (chain-compensated Gasometer). From this, the mixed gases were transferred to Douglas bags.

Gassing is done in a culture room under sterile conditions. From the Douglas bag, the gas is passed by means of rubber and then cotton-packed glass tubes (for bacterial filtration of the gas) into Tyrode's solution in a closed-circuit chamber. Meanwhile, the culture tube is opened, the supernatant fluid is discarded, and new supernatant is added. A glass gassing tube that just touches or dips into the supernatant fluid is inserted into the culture tube in place of the stopper. Gas is passed through the inlet opening, and the culture is gassed for an average of one and one-half minutes at the rate of 2 to 3 liters per minute. Both inlet and outlet are immediately closed (Fig. 1).

Control tubes contained air alone or air and 5% CO_2. After gassing the tubes were put in the rotator inside the incubator.

The number of cultures used in each experiment is indicated in the Table.

The cultures were checked daily under the microscope and were observed as long as there was any evidence of survival (8 to 16 days). A few cultures survived for several weeks.

The following criteria were used in the interpretation of the results: (1) normal growth, (2) arrest of growth and some accumulation of fat (Fig. 2), (3) as above

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From the Departments of Ophthalmology and Physiology, College of Medicine, The State University of Iowa.

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* With 5% CO_2.

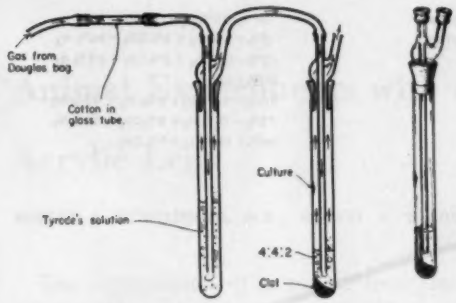

Fig. 1.—Method used in gassing tissue culture. Drawings showing culture during and after gassing.

but with excessive fat accumulation, (4) as above plus some disintegration of the cells and moderate loss of cellular pattern, (5) complete loss of cellular pattern with cellular debris remaining, (6) new growth formation after one or more of the above.

Results

In this study human lens epithelium showed the best growth when air was used. Under 95% N_2 the cultures showed inhibition of growth and some accumulation of fat (Fig. 2). However, there was no disintegration or death of cells. The cultures survived for long periods, and occasionally new growth of cells occurred.

Under 10% O_2 the cultures showed somewhat less growth than under air, and under 5% O_2 the effect was even less favorable.

With the higher oxygen concentrations, 50% O_2, 75% O_2, and 95% O_2 early degenerative changes were noted, the amount of degeneration being parallel to the concentration of oxygen used (Fig. 3).

Number of Gassing Experiments Done and Total Number of Adult Human and Chick Embryo Lens Epithelium Cultures Used

	Experiments, No.		Cultures, No.		Controls, No.	
	Human	Chick	Human	Chick	Human	Chick
1. 95% N_2*	5	1	23	10	11	4
2. 5% O_2+90% N_2*	4		13		9	
3. 10% O_2+85% N_2	4		13		7	
4. 95% air*	1	1	4	10		4
5. 100% air	9+	2+	22+	14+		
6. 50% O_2+45% N_2*	3		7		5	
7. 75% O_2+20% N_2*	3		7		3	
8. 95% O_2*	3	1	7	10	5	10

* With 5% CO_2.

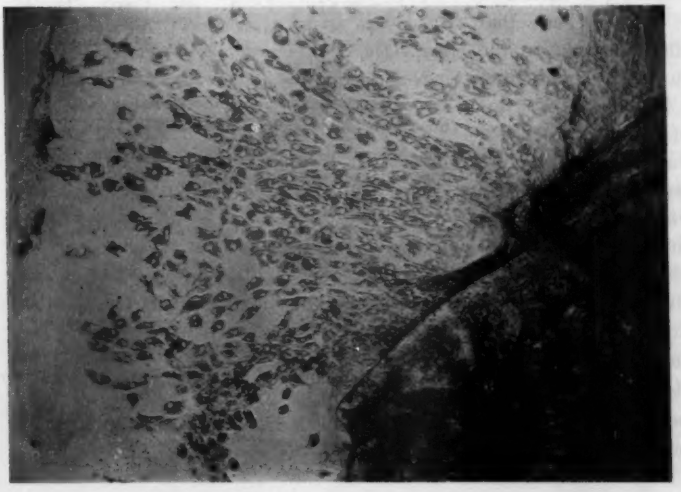

Fig. 2.—Culture of human lens epithelium under 95% N_2+5% CO_2, showing inhibition of growth and some accumulation of fat (12-day-old culture, 6 days of which were under nitrogen).

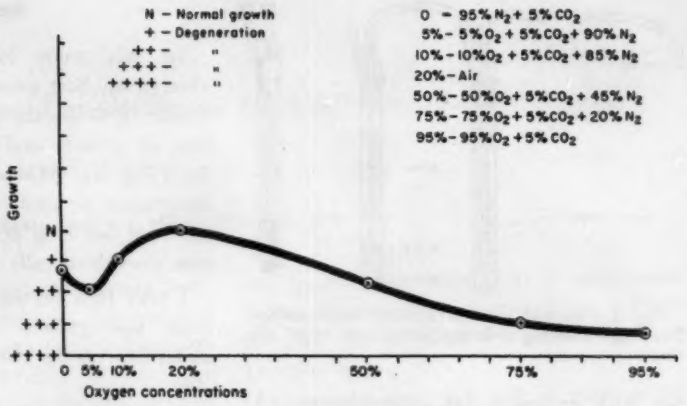
N – Normal growth
+ – Degeneration
++ – "
+++ – "
++++ – "
0 – 95% N_2 + 5% CO_2
5% – 5% O_2 + 5% CO_2 + 90% N_2
10% – 10% O_2 + 5% CO_2 + 85% N_2
20% – Air
50% – 50% O_2 + 5% CO_2 + 45% N_2
75% – 75% O_2 + 5% CO_2 + 20% N_2
95% – 95% O_2 + 5% CO_2
Growth
N
+
++
+++
++++
0 5% 10% 20% 50% 75% 95%
Oxygen concentrations

Fig. 3.—Curve showing the results obtained from the effect of different oxygen tensions used on the growth of adult human lens epithelium in tissue culture.

Chick embryo lens epithelium also showed the best growth in air. It was less able to survive under 95% N_2 than was human epithelium and showed earlier signs of degeneration. It was extremely sensitive to 95% O_2 and showed complete death of cells after 24 hours.

Comment

Best growth occurred when the lens epithelium was grown in air. This indicates that aerobic metabolism plays an important role in these cells. This is in conformity with the findings of other investigators. However, lens cells did survive in an atmosphere of nitrogen, and some growth, although slow in most instances, occurred in many of these cultures. This suggests that glycolysis can supply the energy for the maintenance and growth of the epithelium in the anaerobic state. The reason for increased formation of fat in the cells grown in the anaerobic state has not been determined. When low oxygen concentrations were used, particularly at the level of 5% oxygen, growth was markedly inhibited. This was accompanied by signs of degeneration. This may be due to an inadequate breakdown of carbohydrates, coupled with insufficient oxygen, which could result in inadequate nutrition of the cells. High oxygen concentrations, above 20%, proved unfavorable to the growth of lens epithelium, the degree being proportional to the oxygen concentration.

Summary

Human and chick lens epithelium grow best in culture under aerobic conditions. Growth in culture under anaerobic conditions does occur, though it is much less active, and the accumulation of fat in the cells appears earlier. High oxygen concentrations, above 20%, are unfavorable to the lens epithelium, the amount being proportional to the concentration of oxygen used.

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Animal Experiments with a New Type of Intraocular Acrylic Lens

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The implantation of a plastic lenticulus after removal of a cataract has been a controversial subject from the very beginning. Kirby [1] lists his objections to the Ridley technique as follows: (1) the chemical reaction of a foreign body; (2) the reaction between the lens and the posterior surface of the iris; (3) the pathology which may result from the repeated movement of the lens; (4) the effect of volume and weight of the lens with the eye in motion; (5) the inferior visual results; (6) the protracted inflammatory period.

He further states that, although he prefers not to use the technique at present, he would urge others to continue research on suitable animal eyes. A recent report by Redmond Smith [2] on nine human eyes removed because of intense anterior chamber reaction after Ridley operations also suggests that more animal trials are desirable.

This is a report on experimental surgery on rabbit and dog eyes, in which the lens was extracted and replaced by an acrylic lens fitted into the pupillary opening and held in place by the iris.

Historical Background

The credit for first inserting a plastic lens into the globe following removal of a cataract belongs to Ridley. The date of his first operation is difficult to ascertain from the literature, but the first article concerning it appeared in 1951. When reading his original papers [3-6] one is impressed by the amazing fortune which he had on humans from the very beginning. He deemed animal experiments unnecessary. But in his latest report to date [7] we find that late dislocations into the vitreous are a distinct danger even in extracapsular cases, this having taken place in 4 out of 41 cases. It seems that the posterior capsule must remain fully intact in order to prevent this. Furthermore, the statement is made that it might be desirable to attach the lens to the iris by means of a small hook, which would be placed through the peripheral iridectomy.* This is at variance with his original ideas, in which he attempted to avoid contact between the lenticulus and any moving part in the eye, such as the iris. Perhaps postoperative iritis has also a tendency to form adhesions between the iris and lenticulus and may therefore be actually a desirable feature in order to keep the lenticulus in situ. We therefore see no particular objection to the idea of placing a smaller lens directly into the pupil and having the iris hold it in place by means of a groove placed in the periphery of the lens.

Variously shaped lenses placed into the anterior chamber and resting in the angle have also been devised in Europe, notably those of Strampelli and Schreck. Clouding of the cornea and tilting of the lens are some of the complications which may result. The thought of anything resting against the corneal endothelium near the angle, even to a small extent, does not seem particularly appealing.

Description of the Lens

The first design of this particular type of intraocular lens was made by one of us

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From the Department of Ophthalmology, College of Medical Evangelists.

* Ridley now advocates an anterior chamber lens.

Fig. 1.—Schematic drawing of lens fitted into the pupillary opening and held in place by the iris.

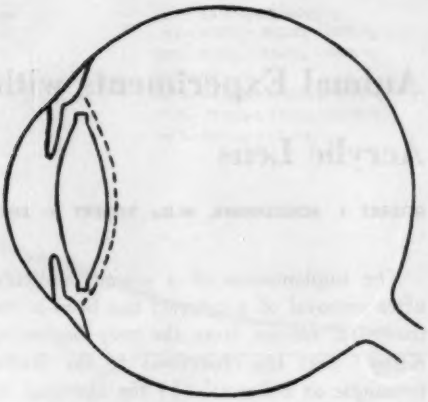

Fig. 2.—Schematic drawing showing the position of the Ridley lens.

(R. J. S.) in May, 1956. Although many variations of it were made, particularly for dogs, only the first (Lens A) and last (Lens X) models will be described here. A drawing of the original lens for use in human eyes is shown in Figure 1. Figure 2 shows the position of the Ridley lens. Figure 3 shows Lens A. This was made by hand from a Lucite rod by one of us (O. R. L.). It had no optics, and its purpose was mainly to determine whether the animal could tolerate it. It was 3.5 mm. thick and 8 mm. in diameter, with a groove in its periphery which was 1.5 mm. wide and 2 mm. deep.

Lens X was a modification of the lens designed by Ridley to fit this new concept. The rim of the lens was ground off, and a groove was made in the periphery 1 mm. wide and 1.25 mm. deep. Figure 4 shows the original and modified Ridley lenses. Although this modification is too small for its intended purposes in the human, its optics made it possible to visualize the fundus in the rabbit.

Mode of Action

A lenticulus situated in the pupil and straddling the iris (Fig. 1) would have the following theoretical advantages: (1) It

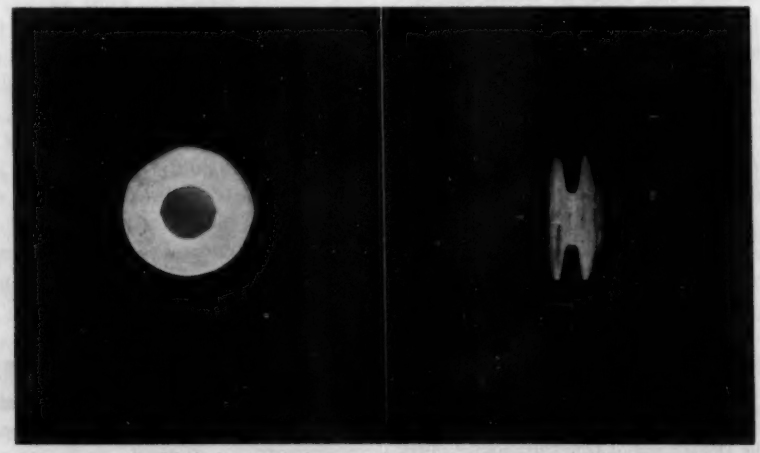

Fig. 3.—Lens A. Made by hand, from methacrylate, it measured 3.5 mm. in thickness and 8 mm. in diameter, with a peripheral groove 1.5 mm. wide and 2 mm. deep.

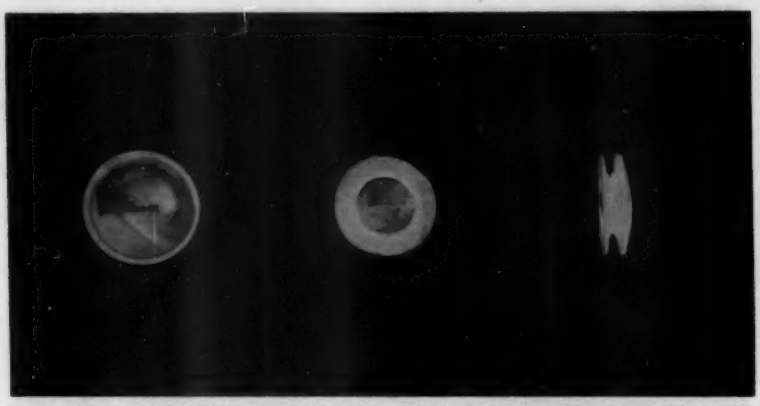

Fig. 4.—The original Ridley lens is shown at left. In the center and at right is Lens X, which is a modification of it made by grinding a groove in its periphery 1 mm. wide and 1.25 mm. deep.

could be used after an intracapsular extraction; (2) it would hold the vitreous back; (3) it might reestablish some form of accommodation if the lens-iris diaphragm were moved forward by squeezing the eye. The obvious disadvantages are tilting and dislocation.

Rabbit Experiments

Seven brown-eyed rabbits were operated upon. Two of them died during or after monocular operation of lens replacement (Rabbits 1 and 2). Rabbit 3 had a Touhy corneal contact lens placed in the anterior chamber in an intact eye in order to observe its effect on the cornea. One week later the cornea was completely cloudy, and, although there was some central clearing later on, the animal was killed five weeks after surgery and the eye was examined microscopically. A pathological report on it is found below. Of the remaining four animals, two had bilateral surgery and the last two, monocular surgery, a total of six eyes in animals which survived the operation. A condensed history of each case

Fig. 5.—Rabbit 4, right eye, showing corneal vascularization.

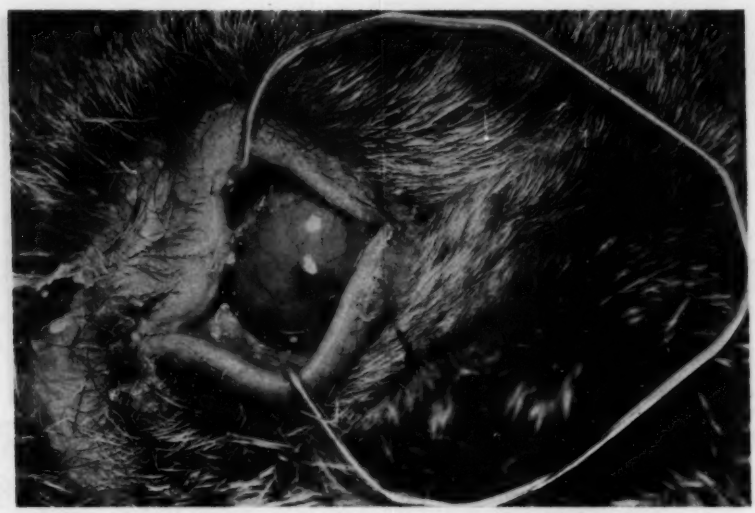

Fig. 6.—Rabbit 4, left eye, showing corneal vascularization.

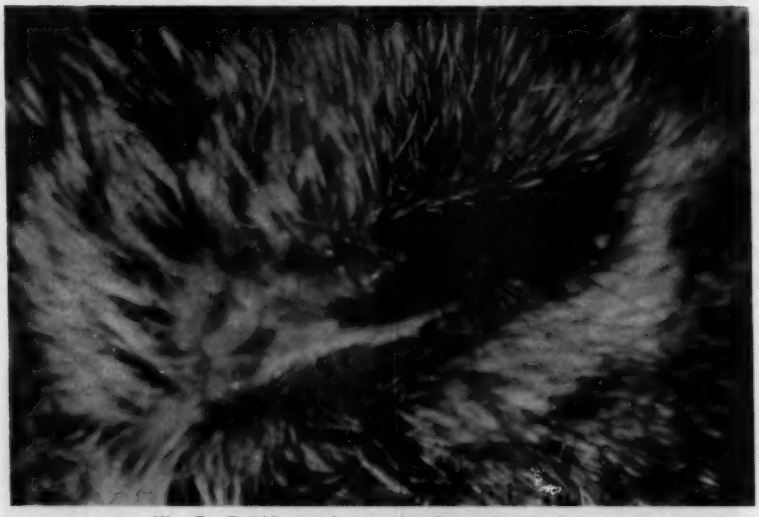

Fig. 7.—Rabbit 4, left eye, showing endophthalmitis.

will be given, but, in order to help the reader's morale, let it be said that the last case did turn out successfully. Perhaps better postoperative care would have given more favorable results, but the distance involved made frequent visits difficult; daily medication was applied by a laboratory technician.

Rabbit 4 was operated upon on Aug. 12, 1956. Anesthesia was 12 mg. of pentobarbital sodium intravenously per pound and ether by inhalation. The bilateral operation performed was corneal section with Graefe knife, no iridectomy, extracapsular lens extraction, insertion of Lens A, five corneal 000000 sutures to close. An ointment containing polymyxin B sulfate, bacitracin, neomyein sulfate, and hydrocortisone (Cortisporin) was applied daily postoperatively. The corneas were clear for a few

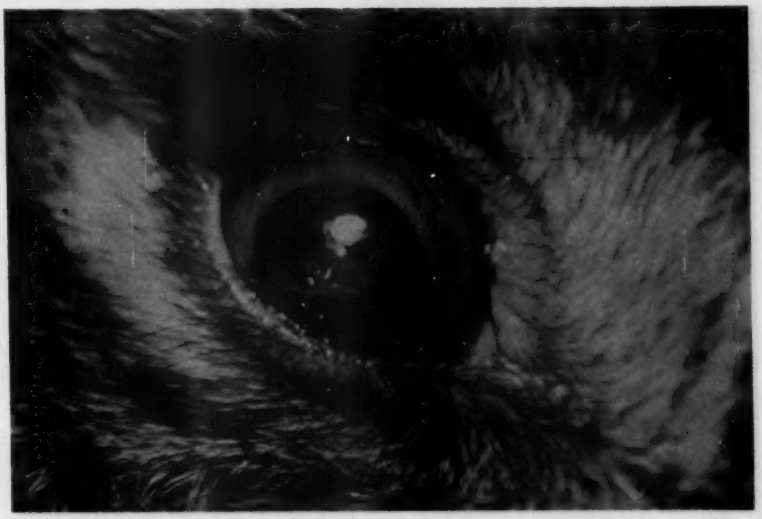

Fig. 8.—Rabbit 4, right eye, showing regression of corneal clouding and vascularization.

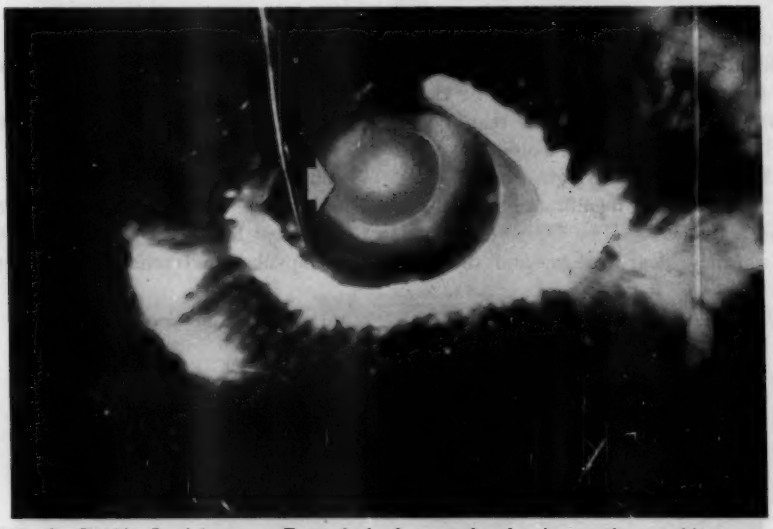

Fig. 9.—Rabbit 5, right eye. Retouched photograph, showing a dense white posterior capsular membrane behind the lenticulus.

days, gradually clouded, and two weeks later were completely opaque. Figures 5 and 6 show the appearance of both eyes on Oct. 16, 1956. Marked corneal vascularization is present, although there is some central clearing in the right. The O. S. developed endophthalmitis (Fig. 7), but the O. D. cleared sufficiently for the lenticulus to be seen. However, it cannot quite be seen in the picture taken Nov. 18, 1956 (Fig. 8). A white membrane fills the pupillary opening. The fundus could never be seen, and the animal died suddenly on Dec. 2, 1956. A pathologic study of the O. D. is given later.

Bilateral operation as described above was performed on Rabbit 5 on Aug. 27, 1956. Posterior pressure in both eyes made

Fig. 10.—Rabbit 5, left eye. Retouched photograph, showing a less dense white posterior capsular membrane behind the lenticulus.

it difficult to close the wounds. The corneas became cloudy within a week, but a month later they began to clear. The clearing continued to such a degree that it was easy to see the lenticuli. Photos taken on Nov. 18, 1956, show the right eye (Fig. 9) with a dense white membrane behind the lens and a hyphema. The O. S. (Fig. 10) shows a fairly clear cornea, and the lens could easily be seen on examination but not in the picture. A thin posterior capsular membrane made it impossible to see the fundus. The animal was killed on Dec. 30, 1956. A pathologic report of the O. S. is given.

Operation on one eye only was performed on Rabbit 6, Nov. 18, 1956. An extracapsular extraction with peripheral

Fig. 11.—Rabbit 6. Retouched photograph, showing dislocation of lenticulus into the anterior chamber.

Fig. 12.—Rabbit 7. Retouched photograph, showing successful implant one week postoperatively.

iridectomy was done, and Lens X was inserted. Cortisone (Cortone) acetate, 10 mg., was injected subconjunctivally immediately after surgery, and pilocarpine was instilled. Cortisporin ointment was applied daily, and treatment with atropine started a week later. One week after surgery the entire cornea was hazy and a posterior capsular membrane and dislocation of the lens in the anterior chamber were noted. The cornea cleared moderately until Jan. 20, 1957. A picture (Fig. 11) taken at that time enables one to see the lenticulus through the hazy cornea; it lies on the sur-

Fig. 13.—Rabbit 7. Retouched photograph, showing successful implant six weeks postoperatively.

Fig. 14.—Dog 4, showing corneal opacification.

face of the iris. Apparently the dense posterior capsule together with lens remnants caused the dislocation.

Rabbit 7 can be considered the only successful result. Surgery was done on Dec. 2, 1956, in the same manner as that on Rabbit 6. One week later the eye was in perfect condition, as shown in Figure 12. The cornea was clear, the anterior chamber formed and deep, and the lens in perfect position in the center of the iris. The fundus could be visualized. However, a week later the cornea began to cloud and treatment with atropine was begun. Gradually the cornea cleared again, and on Jan. 10, 1957, the cornea was practically clear except for scarring in the incision line (Fig. 13). The fundus could be visualized, and the rabbit apparently could see.

Dog Experiments

Six dogs were operated upon, each one on one eye except for Dog 2, who had bilateral surgery. All operations were failures. This statement in the textbook "Canine Surgery," by Lacroix, that "surgery for cataract in the dog has not been generally considered successful" seems to be verified, even though as meticulous a technique as that used in human patients was followed. What induced us to operate on dogs was the report of a successful lens implant to a dog in a popular pictorial magazine, but we have found that it is much easier to operate on a rabbit. Excessive bleeding of all vascular tissues, especially the iris, made the operation very difficult on the dogs, and it is next to impossible to extract the lens in capsule. In view of the bad results the operation was performed in two stages in the last animal. Although the lens extraction itself was successful, the delayed insertion of the lenticulus resulted in failure. The anesthesia consisted of 12 mg. of pentobarbital sodium intramuscularly before operation and ether intratracheally. Retraction of the eyeball during anesthesia makes exposure very difficult in some cases.

In Dog 1 extracapsular lens extraction with complete iridectomy was followed by insertion of a 12 mm. methacrylate (Lucite) sphere. A few days laters the cornea was white, and the dog was used for other, nonocular experiments. Obviously the sphere was too large.

Both eyes of Dog 2 were operated upon on Sept. 23, 1956. A different implant was

used, which consisted of half of a 14 mm. methacrylate sphere, with a groove in the periphery for the iris. Complete iridectomies were performed on both eyes. With much traction and splitting of the zonule, an intracapsular operation was possible on the O. D. Both eyes developed white corneas, flat anterior chambers, and iris prolapses and were lost. This was the only instance in which intracapsular extraction was possible.

Dog 3 had on Sept. 30, 1956, an implant similar to that in Dog 2, on one eye only. This lenticulus also contained two holes for aqueous circulation, since no iridectomy was done. Although no iris prolapse occurred, the cornea turned white within a week and remained so during the two-month follow-up period. A pathologic report is given below.

Dog 4 had the following operation on Oct. 7, 1956. Lens A was modified by drilling a large hole in the center for circulation. No iridectomy was performed. The cornea became cloudy, and a small iris prolapse took place but later healed by scarring. However, the cornea never cleared sufficiently for the lenticulus to be seen. Figure 14 shows the eye as of Dec. 9, 1956, and a pathologic study is found below.

In Dog 5 Lens A was inserted after extracapsular lens extraction, and two peripheral holes were made in the iris with a Ziegler cautery. A large iris prolapse and complete corneal opacification were the result, despite eight corneal sutures.

Extracapsular lens extraction with complete iridectomy and no placement of implant was done on Dog 6, Oct. 21, 1956. A few days later the cornea was hazy, but it cleared completely by Nov. 14, as shown in Figure 15. On Dec. 23, 1956, Lens A was inserted through a corneal incision and placed into the pupillary opening without difficulty. A week later the entire cornea was opaque; then it began to clear again. However, the upper portion remained permanently opaque, and it was impossible to see the lenticulus (Fig. 16).

As can be seen from the foregoing, the implantation of the lenticulus resulted in failure in all of the rabbit experiments except for the one carried out in Rabbit 7. All of the seven dog operations were failures, and they presented additional common complications of iris prolapse, despite tight corneal suturing with Grieshaber needles and 000000 nonabsorbable surgical

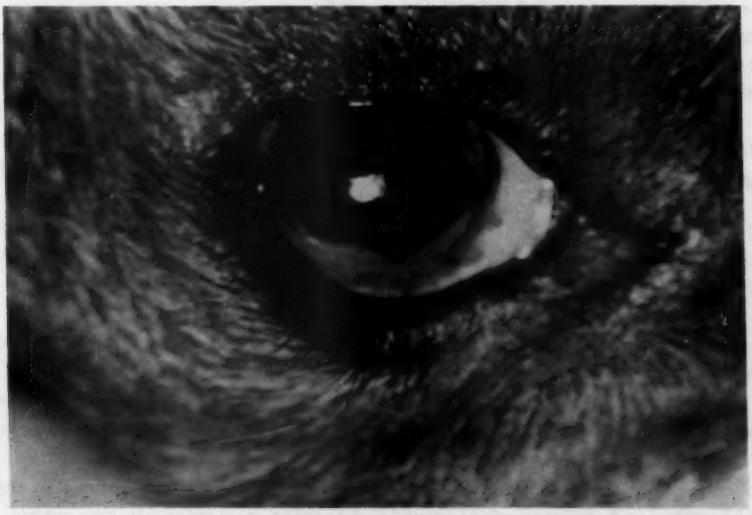

Fig. 15.—Dog 6, after lens extraction only.

Fig. 16.—Dog 6, after delayed implantation of lenticulus, showing corneal clouding, which remained permanent.

(silk) sutures. Pathologic descriptions of some of the enucleated eyes now follow.

Pathologic Study

Paraffin sections were made of the eyes mentioned above after first dissolving the acrylic lenses in chloroform, and the slides were stained with hematoxylin and eosin.

Rabbit 3.—This specimen consisted of an atrophic right eye measuring 14×17×18 mm. The cornea is sectioned transversely, with the larger calotte below. The cornea is opaque and is in contact with the iris through its entire circumference. A dense coagulum extends backward from the lens, detaching the major portion of the retina. Under microscopic study the cornea shows areas of stromal thickening, with hypertrophy of the epithelium. A fibrotic coagulum type of tissue appears to be present with the endothelium. This membrane extends to and covers the surface of the iris, on which a further band attaches to a portion of the retina, causing a detachment. The retina, choroid, and sclera appear normal.

Rabbit 4.—The right eye measures 11×18×17 mm. and is sectioned transversely, with the larger calotte below. The cornea is opaque and in contact with the iris in its entire circumference. The remnant of the softened acrylic lenticulus lies posteriorly in the vitreous cavity. All of the retina seems to be in place, with the exception of an area where a fibrinous band reaches from lens to retina. Under microscopic examination the cornea shows considerable edema, with thickening of the epithelium and clefts in the stromal layer. The iris lies in contact with the endothelium. The angles are completely blocked. The iris itself is moderately thickened, with some round-cell infiltration. The pigment layer is considerably disturbed, with evidence of fibrinous proliferation, probably as a result of its contact with the acrylic lens. The lens itself has been displaced into the vitreous body. The retinal layers are intact and normal.

Rabbit 5.—The left globe appears atrophic, measuring 8×18×17 mm. The section is taken transversely, with the larger calotte below. The cornea is opaque. The anterior chamber is well formed. A coagulum extends from the lens to the retina, detaching a portion of the retina. Micro-

scopic examination shows that considerable round-cell infiltration is present in spotted areas of the cornea. The endothelium is broken and the epithelium thickened. The iris is in contact with the cornea over a major portion of its surface. The fibrous coagulum extends into the vitreous, from which an adhesive band is attached to the retina, detaching it throughout the major portion of its area. The retinal, choroidal, and scleral areas are intact.

Dog 3.—The specimen is that of a left eye measuring 21×23×23 mm. The cornea is round, 15 mm. in diameter, and opaque, preventing the visualization of the interior of the eye from above. The eye is sectioned horizontally, with the larger calotte above. The interior of the eye shows the anterior chamber to be filled with a coagulum and the center of the cornea to be in contact with a membrane. There is no evidence of any acrylic lens implant. The retina is in place, but there is a coagulum running from the equator forward to the pupillary membrane in the inferior portion of the globe. Under microscopic study the corneal stroma shows areas of edema and the epithelium is thickened in spots. The endothelium has been disrupted, and in contact with it is a fibrotic type of tissue over its major surface. The iris itself is in contact with the cornea in places. The retina, choroid, and sclera appear within normal limits.

Dog 4.—The specimen measures 22×21×20 mm. The larger calotte is taken inferiorly. The cornea appears cloudy. The anterior chamber appears of normal depth. The softened acrylic implant appears to be present and in place in the pupillary area. A coagulum extends from this area to the ora in all directions. The retina appears normal and in position. Microscopic examination shows the cornea to be thickened. There are breaks in the endothelium, with localized areas of edema of the stroma, with breaks in Bowman's membrane and thickening in the epithelium. The iris is in contact with the cornea in one area, in which

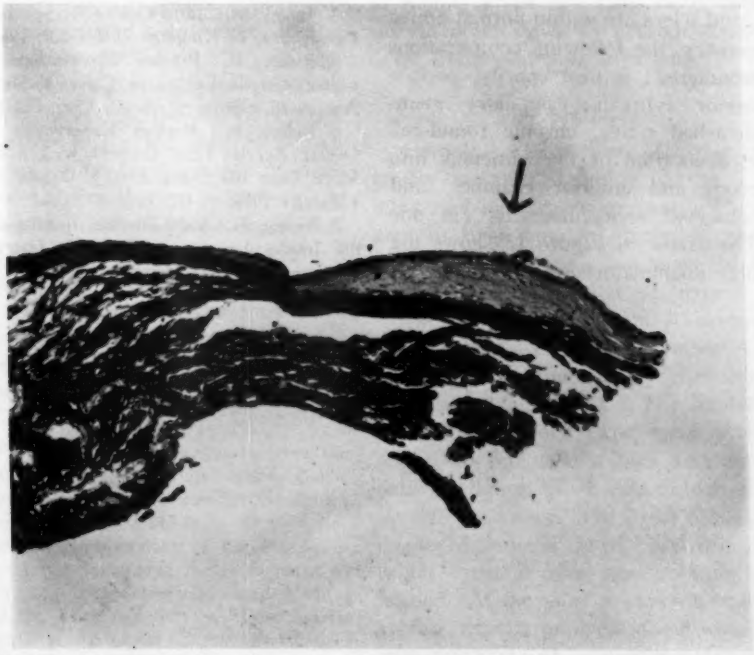

Fig. 17.—The arrow shows the typical fibroinflammatory reaction produced by contact of the iris with the implant in a dog eye.

there is some fibrous reaction and an increase in round cells. The iris itself shows a minimal amount of foreign-body reaction, however. The retina, choroid, and sclera are intact.

Dog 6.—The eye measures 20×21×21 mm. The cornea is opaque, measuring 14 mm. in diameter. The globe is sectioned transversely, with the larger calotte below. The anterior chamber is formed and of normal depth. The remnants of the softened acrylic lens implant are still present, with the iris in its groove. Posterior to the implant there is an opaque cyclitic membrane. The vitreous appears clear, and the retina is in place. Under microscopic examination the cornea appears intact, with an anterior chamber of normal depth. The angles are open. The iris is somewhat distorted, showing a fibrous covering over the surface of both pigment epithelium and anterior layers, obviously in an area where the acrylic lens implant was in contact. Posterior to this is a moderately dense cyclitic membrane, with remnants of lens tissue. The retina, choroid, and sclera are within normal limits.

In summary, the following complications were encountered: corneal opacity, peripheral anterior synechiae, pupillary membrane, detached retina, chronic round-cell response, dislocation of the lenticulus into the vitreous and anterior chamber, and grossly observed endophthalmitis (in one case). The arrow in Figure 17 shows the typical fibroinflammatory reaction produced by contact of the iris with the implant in a dog's eye.

Summary

The use of a new type of acrylic intraocular lens in rabbits and dogs is described. This lens fits into the pupillary opening and is held in place by the iris by means of a peripheral groove. Successful implantation was accomplished in only one of six rabbit eyes and in none of seven dog eyes. The complications encountered are described, together with pathologic studies.

727 W. 7th St. (17).

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Uveitis in Rabbits with Experimental Allergic Encephalomyelitis

Results Produced by Injection of Nervous Tissue and Adjuvants

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Although much experimental work has been done on endogenous uveitis, there have been relatively few successful animal experiments in which eye disease is produced without direct manipulation of the eye itself. Two recently reported techniques for producing uveitis experimentally show some promise of contributing to our understanding of disease of this type. Collins [1,2] has described a uveitis, said to resemble sympathetic ophthalmia, in guinea pigs and monkeys sensitized with uveal tissue and the so-called "Freund adjuvants" (killed tubercle bacilli and mineral oil). Uveitis has also been reported to occur (Fog and Bardram [3]) in pigs with experimental allergic encephalomyelitis (EAE), an experimental demyelinative disease produced by giving animals inoculations of central nervous system antigen plus adjuvants.[4] In both these experiments, a number of lines of evidence suggest that an autoallergy is produced, in the first case with some component of uveal tissue as the antigen and in the second with a constituent of normal myelin. It is not clear, in the second instance, why uveitis should occur in animals in which disease of the nervous system appears to be the primary event.

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In the course of experiments designed to investigate the nature of the EAE which might be produced in rabbits by giving them injections of optic nerve and adjuvants, we observed a grossly recognizable uveitis, in confirmation of Fog and Bardram's findings. Since the publication of these authors was based on histological observations in only two animals, and since our own findings were obtained in another animal species, it seemed desirable to summarize the results of a series of experiments in which both the eyes and the nervous system were studied clinically and histologically in rabbits given injections of optic nerve, several other types of nervous tissue, and uveal tissue—all plus adjuvants.

Methods

Animals.—Albino New Zealand rabbits, mostly females, weighing 2.5 to 3.5 kg., were used in these experiments. They were kept in large bins in groups of about 10 or in individual cages and were fed Purina Rabbit Chow and water ad libitum.

Antigens and Inoculation.—Various types of nervous tissue were removed from healthy animals immediately after death and were stored at −20 C. The human optic nerve used in one experiment was taken within a few hours post mortem from patients dying of disease which did not involve this tissue. The uveal tissue antigen employed was the choroid and iris of fresh rabbit eyes; it was stored similarly until needed. At the time of experimentation the frozen nervous or uveal tissue was thawed, superficial fat and connective tissue (including meninges) were removed by dissection,

and the tissue was washed several times in sterile saline solution to remove all traces of blood. The optic and sciatic nerves were cut twice on a freezing microtome to break up connective tissue. Two parts of whole nervous or uveal tissue were then ground in a mortar with three parts of mineral oil containing 3 mg. per milliliter of killed tubercle bacilli.* In one experiment a total lipid extract[5] of rabbit spinal cord was used, the amount employed in the injection mixture having been prepared from the correct weight of fresh tissue. All rabbits were given inoculations of 0.05 to 0.1 ml. amounts of antigenic mixture injected intradermally into one or more toe pads. This technique is effective in producing allergic encephalomyelitis in the majority of animals given injections.

Clinical Observations.—Following inoculation, the rabbits were observed daily for a period of approximately six weeks. They were forced to run and jump, so that their neurological status could be appraised, and their eyes were examined for gross evidence of disease. When such evidence was observed, the eyes were examined further with the ophthalmoscope and the slit lamp. In experiments where optic nerve or uveal antigens had been injected, all animals were examined daily with the slit lamp and the ophthalmoscope, regardless of whether or not gross signs of eye disease were present. After disease of the eyes or nervous system had been present for several days, or at the end of a six-week observation period, the rabbits were killed and tissues were removed for histological study.

Histological Observations.—In the majority of experiments, one or both eyes were studied histologically. In addition, in almost all cases, the optic nerves, the brain, and the spinal cord together with its roots and ganglia were also removed. The sciatic nerves were studied in particular experiments. Formalin-fixed tissues were routinely stained with hematoxylin and eosin. Additional sections of positive eyes were stained with the Loyez technique (for myelin), the oil red O stain (for neutral fat), the Gros-Bielschowsky method (for axis cylinders), Verhoeff's stain (for elastic tissue), and the hematoxylin and Van Gieson method (for connective tissue).

* Heat-killed tubercle bacilli of the Jamaica 22 strain, obtained from Dr. Jules Freund.

TABLE 1.—*Summary of Experiments in Which Eyes Were Examined*

Inoculation Antigen	Rabbits, No.	EAE			No. with Eye Disease	
		No.	Average Onset, Day	Histological Severity	Clinical	Histological *
Rabbit optic nerve †	4	4	13	++	3	3
	4	2	12	++++	2	2
	4	2	17	+++	0	3
	3	1	15	--	1	--
	4	4	--	+	0	0
Rabbit uvea	7	1	16	+	0	0
Rabbit brain	4	3	14	++	1	--
Rabbit cord	4	3	15	--	0	0/1
	8	3	23	++	0	--
	23	10	16	+++	1	3/7
	4	2	14	--	0	1/2
Total lipid extract of rabbit cord	4	3	22	+++	0	1
Bovine optic nerve	4	2	26	++	0	0
Bovine white matter	12	11	13	+++	0	0/1
	4	4	10	+++	0	2
Bovine white matter, autoclaved	3	3	11	++++	0	2
Bovine sciatic nerve	9	8	12	++++ ‡	0	0
Human optic nerve	4	4	24	++	0	2
Dog optic nerve	4	4	16	+++	2	3

* Excluding eye lesions in animals with Encephalitozoon (Table 2). Eyes were examined of all animals in an experiment unless otherwise indicated. An unfilled space indicates that the material was not examined histologically.
† In this experiment, five littermate controls inoculated with tubercle bacilli in oil but no nervous tissue failed to develop any sign of eye disease.
‡ EAN, disease involving only the peripheral nervous system.

TABLE 2.—*Summary of Clinical and Histological Findings in Individual Rabbits Developing Eye Disease*

Inoculation Antigen	Experimental Allergic Encephalomyelitis			Clinical Eye Disease			Histological Eye Disease *		
	Onset	Severity	Optic Neuritis	Onset	Duration	Severity	Day Eye Removed	Nerve Head & Retina	Iris & Ciliary Body
Rabbit optic nerve	17	++	++	17	2	+	22	±	++
	11	+++	--	11	3	+	13	--	++
	10	+++	+++	10	4	++	13	+++	++
	10	+++	+++	10	3	+++	12	+++	+++
	14	++	+++	14	2	+	15	++	+
	14	++	++	None			21	±	+
	--	0	+	None			31	+	±
	15	+	++	None			21	0	+
	15	++	--	16	1	+	--	--	--
Rabbit brain	17	++	--	12	2	+	--	--	--
Rabbit spinal cord	11	+	0	None			23	0	0
	9	+ †	0	9	3	+	20	+	±
	11	++	++	None			23	+	0
	16	+	+	None			21	+	±
	13	+++	--	None			14	+	0
Rabbit cord lipids	42?	+	++	None			48	+++	0
Bovine optic nerve	16	+ †	+	None			39	0	+
Bovine white matter	9	+++ †	+++	None			9	+	+
	9	+++	++	None			10	+	++
Autoclaved bovine white matter	9	++	+	None			11	+	0
	9	+++	++	None			16	+	++
Bovine sciatic nerve ‡	9	+++ †	0	None			12	+	++
	9	+++ †	0	None			12	0	+
Human optic nerve	24	+	0	None			60	+	+
	24	+++	0	None			30	+	0
Dog optic nerve	11	++	--	16	3	+	20	±	±
	15	+++	+	17	3	+	20	±	0
	--	+	+	None			35	+	±

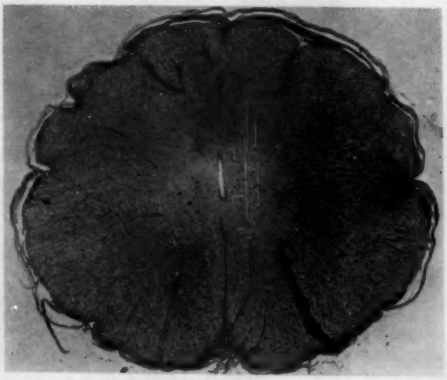
* An unfilled space indicates that the material was not examined histologically.
† Encephalitozoon lesions were found in the central nervous system or elsewhere. Encephalitozoon lesions were also found in 3 of the 36 rabbits not showing eye disease.
‡ EAN, disease involving only the peripheral nervous system.

Results

Table 1 is a summary of the types of tissue injected and the results obtained in all our experiments. In Table 2 the detailed clinical and histological findings in individual rabbits which showed evidence of eye disease are reported.

Injection of optic nerve or other central nervous tissue with adjuvants produced typical experimental allergic encephalomyelitis (EAE) in a high percentage of the rabbits. Injection of uveal tissue also produced EAE in one animal out of seven. Injection of peripheral nerve produced experimental allergic neuritis (EAN). Both EAE and EAN have been described elsewhere [4,6] in great detail. The former is a progressive neurological disease characterized by paralysis, ataxia, and loss of sphincter control; the latter is a more transient disease, consisting mainly of ataxia accompanied by some weakness. In all cases,

Fig. 1.—Low-power view of typical EAE lesions in the rabbit spinal cord. There are moderate inflammatory infiltrates about the veins and distributed beneath the pia. A mild meningitis is also present. The principal cells in these infiltrates are histiocytes and lymphocytes. Hematoxylin and eosin. (Reproduced from Waksman and Adams,[6] *The Journal of Experimental Medicine*, The Rockefeller Institute for Medical Research, Baltimore.)



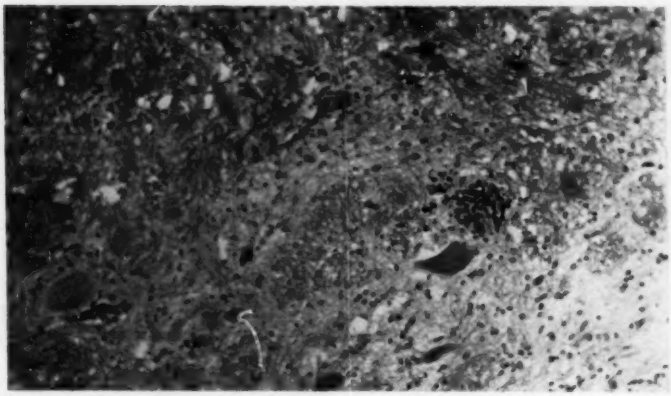
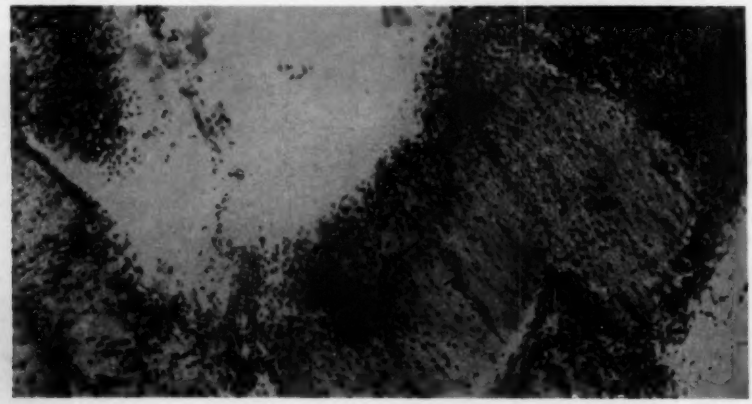


Fig. 2.—Perivenous accumulations of histiocytes in the cerebellar peduncle of Rabbit 19, killed four days after the onset of EAE. These cells are almost epithelioid in appearance. Hematoxylin and eosin; reduced about 12% from mag. × 125.

disease occurred 10 to 26 days after inoculation, with an average onset at approximately 14 days. Microscopic examination of the nervous system revealed characteristic lesions comparable to those described in the literature dealing with these experimental diseases. Focal perivenous aggregates of histiocytes and lymphocytes, accompanied by clear-cut demyelination, were found, scattered throughout the white matter of the central and peripheral nervous system in EAE and limited to the spinal roots, sensory ganglia, and peripheral nerves in EAN (Figs. 1 and 2). Lesions of the optic nerves and chiasm were found in the great majority of animals with EAE (Fig. 3).

With the appearance of EAE, some of the animals developed ocular disease, which reached peak severity when the EAE was most pronounced. Clinically, conjunctivitis, miosis, and iridocyclitis were present. Conjunctivitis is considered part of a definite disease complex in these experiments, despite the well-known tendency of rodents to have conjunctival inflammation. In the cases recorded here as showing this change, the conjunctivae were normal until the onset of EAE. In some rabbits, although clinical eye disease was not observed, there was histological evidence of disease. Slit-lamp examination showed flare, cells in the anterior chamber, iris vessel dilatation, and fibrinous or cellular deposits on the anterior lens surface. Even in the most severely affected eyes, these changes were never more than mild to moderate. Ophthalmoscopy did not

Fig. 3.—Inflammatory reaction in the optic chiasm of Rabbit 389 (inoculated with rabbit optic nerve, onset of 3+ EAE at 14 days) on second day of disease. The cells are predominantly histiocytes. Hematoxylin and eosin; reduced about 26% from mag. × 125.



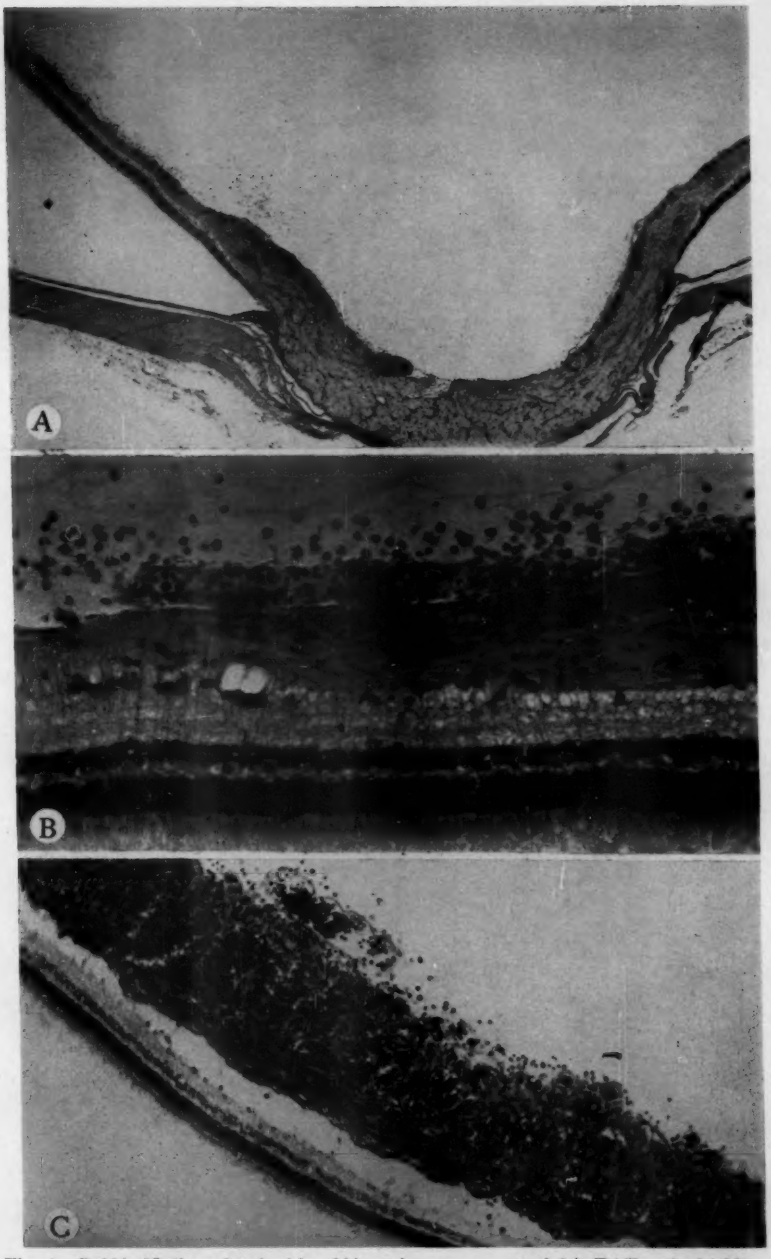


Fig. 4.—Rabbit 85 (inoculated with rabbit optic nerve, onset of 3+ EAE and of iridocyclitis on 10th day), findings on 3rd day of disease. *A*, optic papilla and retina. There is an intense inflammatory reaction which is perivascular in the optic papilla and extends diffusely into the nerve-fiber layer of the retina. Hematoxylin and eosin; reduced about 13% from mag. × 37. *B*, higher-power view of the same lesion. The cellular make-up of the inflammatory infiltrate is comparable to that seen in lesions of other parts of the nervous system. Hematoxylin and eosin; reduced about 13% from mag. × 400. *C*, myelin stain of the same lesion near the optic papilla. There is perivascular demyelination in the area affected, particularly near the surface of the nerve-fiber layer. Loyez stain; reduced about 13% from mag. × 125.

reveal any definite abnormality of the fundus.

The ocular histologic changes appeared to be of two main types. In one the optic papilla showed a dense infiltrate of histiocytes and lymphocytes which extended along the nerve-fiber layer of the retina. In mild cases these infiltrates were clearly perivascular. In some cases the involved areas failed to take the myelin stain and yet the axis cylinders appeared to be well preserved. These lesions, which appeared to be characteristic EAE lesions of myelinated nervous tissue, are illustrated in Figure 4. The second type of change consisted of discrete perivascular nodules of the iris and the ciliary body, made up almost entirely of histiocytes (Fig. 5). Myelin and axis-cyl-

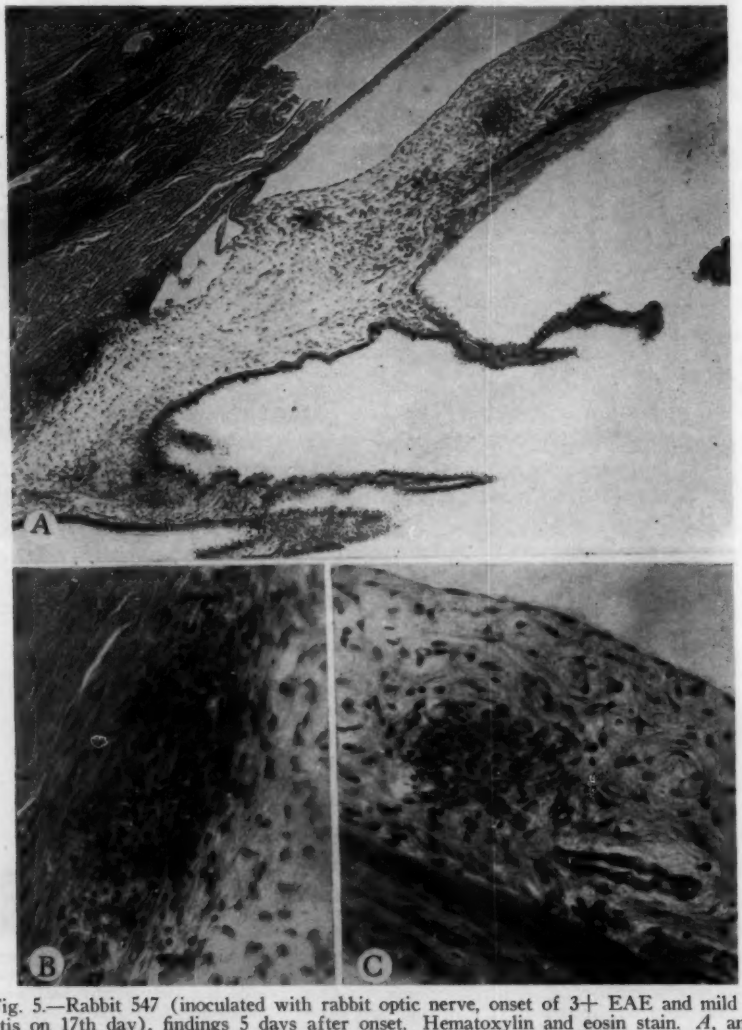


Fig. 5.—Rabbit 547 (inoculated with rabbit optic nerve, onset of 3+ EAE and mild iridocyclitis on 17th day), findings 5 days after onset. Hematoxylin and eosin stain. *A*, anterior uveal segment; reduced about 13% from mag. × 100. Discrete perivascular nodules are seen in the iris and ciliary body. *B* and *C*, higher-power view of lesions in the ciliary body and iris. The cellular aggregates are composed of lymphocytes and histiocytes; reduced about 13% from mag. × 300.

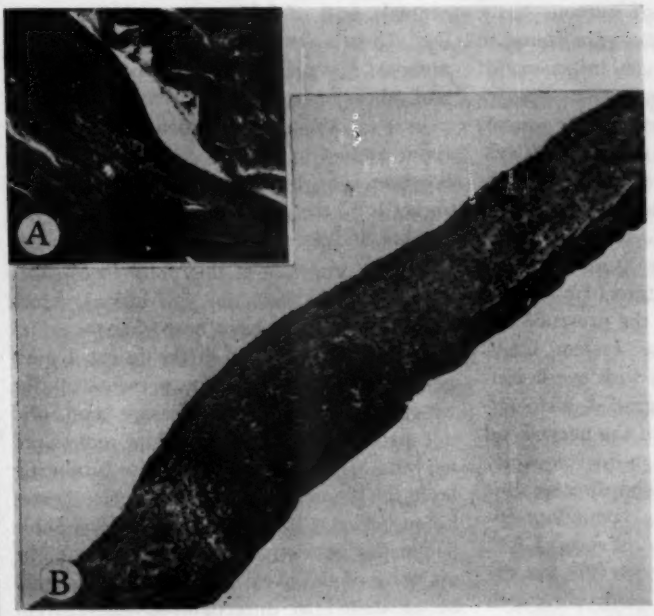


Fig. 6.—Rabbit 35 (inoculated with bovine optic nerve, 1+ EAE). This animal had no clinical eye disease, and no histological lesions were found in the optic chiasm or optic papilla. Encephalitozoon lesions were present in the brain. The limbal infiltrate and solitary iris nodule illustrated in *A* and *B* are believed to be lesions produced by this parasite. Hematoxylin and eosin; × 100.

inder stains failed to demonstrate any abnormalities in relation to these lesions. The choroid did not appear to be affected at all. Similar cell collections were frequently observed in the extraocular muscles and the limbus, but no significance was attached to these because of their frequent occurrence in "normal" animals.

In 8 of 64 rabbits examined histologically, characteristic granulomatous lesions were found in the cerebral cortex or elsewhere in the central nervous system gray matter. These appeared to be typical lesions produced by Encephalitozoon cuniculi, a common protozoon parasite of the rabbit related to toxoplasma.[7] In three of these animals no eye disease was found. Of the five with eye disease, one presented a perivascular scleral lesion in addition to iritis, while a second showed a large isolated iris nodule accompanied by a very heavy limbal infiltration (Fig. 6). Still another was an animal with EAN, in which there was no reason to expect uveitis (see Comment). We must of necessity attribute these lesions to the parasite. In the remaining two animals there were iris or retinal lesions similar to those seen in other animals of these experiments.

TABLE 3.—*Number of Rabbits with Intraocular Disease in Relation to Severity of EAE*

Eye Findings (Histological)	Severity of EAE (Histological)			
	0	+	++	+++
Disease *	1	7	7	9
No disease	14	8	5	5

* Excludes cases with Encephalitozoon infection.

The relation of the iridocyclitis observed to the nature of the injected material, on the one hand, and to the nature of the disease in the nervous system, on the other, can be determined from the data presented in Tables 1, 3, and 4. There appeared to be no correlation between the presence of

TABLE 4.—*Correlation of Intraocular and Extraocular Optic Neuritis with Iridocyclitis*

EAE Involvement of		Eyes Examined	EAE of Optic Nerve Head or Retina		No Disease of Optic Nerve Head or Retina	
CNS	Optic Chiasm *		Iridocyclitis	None	Iridocyclitis	None
+	+	26	10	4	2	10
+	0	16	3	2	0	11
0	+	2	2	0	0	0
0	0	7	0	0	0	7

* The optic nerve and chiasm were examined in 123 rabbits, of which 70 had EAE; 50 of the animals with disease presented lesions of the optic chiasm.

eye disease and the type of nervous tissue injected. Intraocular lesions were found in about half the animals given injections of optic nerve derived from various species and in a similar proportion of animals which received other central nervous system material. Uveitis did not occur in rabbits given homologous uveal tissue with adjuvants (one of these developed mild EAE) or adjuvants alone. On the other hand, the presence of intraocular disease was clearly correlated with the presence and severity of central nervous system EAE. Three-quarters of the cases with eye lesions were animals with EAE graded histologically as 2+ or 3+. EAE of the nerve head and retina occurred rather more frequently when the optic chiasm showed disease; this finding perhaps reflects the commoner involvement of the chiasm in severer EAE. The most striking finding, however, was the unmistakable correlation of iridocyclitis with disease of the nerve head and retina: In only 2 of 17 animals with this type of change did we fail to find EAE within the eye.

Comment

A number of specific points seem to be established by our data. Optic nerve injected with adjuvants produces EAE comparable to that produced with any other material derived from the central nervous system. In EAE in the rabbit, optic neuritis, as judged by lesions seen in the chiasm, is frequent; it was present in approximately 70% of the animals with EAE which we examined. EAE lesions occur in the myelinated nervous tissue within the eye in over half the animals in which this experimental disease is produced, particularly in the severer cases. Mild to moderate iridocyclitis is present in a large proportion of these animals with intraocular EAE. This finding confirms Fog and Bardram's observation in the pig.[3] In rabbits with EAN, in which no intraocular nervous disease occurs, no uveitis is seen. In rabbits injected with homologous uveal tissue plus adjuvants, EAE is produced in occasional animals, in 1 of 7 in our experiment and in 2 of 18 in a series reported by Suie.[8] This antigen, however, did not produce uveitis, and others [8,9] have similarly failed to obtain uveitis in rabbits by sensitization with uveal tissue and adjuvants. The same experiment, however, has been reported by Collins to succeed in the guinea pig and monkey,[1,2] but his finding awaits confirmation.[10]

It is appropriate at this point to consider the possibility that the eye lesions which we observed may have been due to an infectious agent present in the injected antigen mixture or already present in the experimental animals. Adjuvant alone did not produce eye disease, while autoclaved nervous tissue was effective in producing both EAE and uveitis. The precise correlation between the uveitis and EAE (Table 4) makes it extremely doubtful that the majority of the uveal lesions observed could be attributed to unrecognized intercurrent infection, such as by Encephalitozoon. The great majority of animals with eye disease had no lesions produced by this parasite in the cerebral cortex, the most frequently affected site, or elsewhere in the nervous system; nor did they show choroidal or scleral lesions. The obvious onset of clinical eye disease in conjunction with the onset of encephalomyelitis, seen in a number of cases, cannot be explained on the grounds of intercurrent disease.

The pathogenetic mechanism involved in the production of EAE and EAN cannot be discussed in detail here (see reviews [4,11,12]). These entities are representatives of a group of experimental autoallergies, which can be produced with seven different tissues (central nervous system myelin, peripheral nervous system myelin, lens, uveal tissue, testis, thyroid, and epidermis). In each instance the antigen appears to be organ-specific, i. e., the same or closely similar antigenic substances are present in a variety of species. Thus, in the present experiments (Table 1) EAE occurred in rabbits injected with rabbit, bovine, canine, and human nervous tissue.

While a single highly purified antigenic substance has not been isolated, much progress has been reported in the purification of the antigen.[5,13-16] It appears probable that a hypersensitive reaction of the delayed or tuberculin type, rather than circulating antibody, may be responsible for the production of EAE,[17] but the mechanism cannot be properly investigated without the use of single pure antigen.

There is now evidence that the actual development of EAE lesions at a given site may depend not only on the presence of a sufficiently intense general sensitization but on local factors such as the permeability of blood-tissue barriers to antibody or antibody-carrying cells.[18] The presence of intraocular EAE lesions in less than 100% of rabbits with EAE must depend on such local factors, as must the fact that a particular antigen, such as bovine optic nerve, appears (in an experiment with only four rabbits) unable to produce eye disease. The presence and concentration of the antigen, in this case myelin within the eye, is another local factor which may determine the frequency with which characteristic intraocular lesions occur. In other species, with more or less myelin in the retina, different results would surely be obtained.

The nature and mechanism of production of lesions in the ciliary body and iris in animals with intraocular EAE is the most challenging question raised by the present group of observations. There would appear to be at least three possibilities. The reaction may be simply an EAE response to myelin present in nerves which supply the iris and ciliary body. However, no uveal reaction was observed in animals with intense EAN, in which the peripheral nerve is the main site of the lesion. A second possibility is that uveal tissue contains substances which are antigenically closely similar to the antigens of central nervous system myelin. This hypothesis is supported by the production of uveitis in animals injected with nervous tissue and the production of EAE in animals injected with uveal tissue. Indeed, the second finding is difficult to explain otherwise; the initial dissection of the uveal tissue used for injection was sufficiently thorough to leave essentially no retinal tissue attached. The failure of uveal tissue injection to produce uveitis, however, argues against both hypotheses. The last possibility is that the iridocyclitis is a secondary event consequent to the inflammatory disease involving the retina. As the venous drainage of the optic papilla and the nerve-fiber layer of the retina is independent of the vascular supply of the anterior uveal segment, this seems highly unlikely, unless one postulates the diffusion of inflammatory products across the vitreous. Whichever of these three mechanisms is finally accepted, it must explain the complete absence of choroidal involvement in this type of experiment.

The relationship between the uveitis associated with EAE and human uveitis must remain purely speculative at this time. Uveitis associated with optic neuritis or with neuroretinitis is said to occur in man.[19] Neuroretinitis has been reported in a number of cases of measles [20-23] and, like optic neuritis, is regarded as a manifestation of measles encephalitis. EAE is generally regarded as a satisfactory experimental model for the acute encephalomyelitis associated with measles and other exanthemata. It is of considerable interest that unilateral or bilateral uveitis has been observed in cases of measles, mumps, and chickenpox.[24-26] Rucker [27] has reported that 10% to 20% of patients with multiple sclerosis show a sheathing of the retinal veins, but the validity of this finding has not been definitely established. Such a change may well be similar to the intraocular EAE observed in the present experiments. Further research is needed to clarify the relationship between the experimental uveitis in our rabbits and such types of disease as sympathetic ophthalmia, the Vogt-Koyanagi syndrome, and Harada's disease, in which the eye disease is frequently accompanied by involvement of the central nervous system.

For the moment, the autoallergic uveitis reported by Collins [1,2] would seem to provide a somewhat better model for these processes. Other types of "endogenous uveitis" are not usually associated with encephalomyelitis, but they, too, may occasionally be accompanied by abnormalities of the cerebrospinal fluid.

Summary

Rabbits given injections of optic nerve of various animal species together with the Freund adjuvants (killed tubercle bacilli and mineral oil) developed typical experimental allergic encephalomyelitis (EAE) comparable to that produced with other types of central nervous tissue.

In animals with EAE optic neuritis was frequently present, and in a considerable proportion of cases it involved the optic papilla and the nerve-fiber layer of the retina.

A mild to moderate iridocyclitis occurred in about three-quarters of the animals with intraocular EAE, its onset coinciding with the onset of EAE.

In rabbits with experimental allergic neuritis, produced by injection of peripheral nerve with adjuvants, no intraocular lesions were found.

Injection of whole rabbit uvea with adjuvants produced EAE in one animal out of seven but failed to produce uveitis.

Drs. David Cogan, Irwin Mancall, and David Johnson participated in the earlier phases of this investigation. Margaret Carroll, Nancy Schaeffer, Beverly Brooks, and Donald Gaulitz gave technical assistance.

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Annual Reviews

The Uveal Tract

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The voluminous literature concerned with the uveal tract continues to offer studies that contribute to our understanding of the reaction of this tissue to disease as well as of its normal function. Most of the reported works pertain to inflammatory diseases of the uveal tract; however anatomy and physiology continue to interest many workers.

Anatomy

By studying flat frozen sections it was found by Rohen [1] that the anterior fibers of the ciliary body are almost exclusively composed of elastic fibers that turn at right angles before joining into the trabecular meshwork. Some of these fibers enter into the scleral spur and help to form the base of Schlemm's canal. It is postulated that movement of these fibers influences the function of Schlemm's canal.

Flocks,[2] in his study of the trabecular meshwork, examined the trabeculae by serial tangential sections. Through this study it was found that three distinct anatomical structures make up the meshwork. The innermost portion is the uveal part, composed of a collagen core covered with endothelium. The second layer is the corneoscleral portion. These lamellae are composed of flattened collagen fibers running perpendicular to the longitudinal ciliary muscle. Openings between the trabeculae are smaller in the corneoscleral portion than in the uveal lamella. The third layer is the pore tissue that lines Schlemm's canal. The exact nature of this layer is difficult to determine, owing to the irregularity of the wall of Schlemm's canal. Further study of this important area may give us a better understanding as to the function and pathology of the filtration system and would increase our knowledge of the cause of glaucoma.

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Calamandrei and Camici [3] studied Bruch's membrane with particular reference to the elastic component. The study confirms the general belief that the elastic portion belongs to the capillary tissue of the choroid. The elastic membrane is said to extend as far forward as the ora serrata. As a result of this and previous studies, it is concluded that Bruch's membrane is part choroid and part retina. The division between the cuticular and elastic element is the division between choroid and retina.

The movements of the iris are controlled by two independent variables. One is the parasympathetic innervation, which varies swiftly through wide limits. The other is the sympathetic, which varies slowly through narrow limits. In his study, Apter [4] found that important reflexes, such as those of convergence, divergence, and accommodation to light and darkness, are parasympathetic. Vasoconstriction, whatever the cause, dilates the pupil. In fact, the sympathetic control of the dilator is not sufficient to overcome the parasympathetic action.

According to Shimoyama [5] certain ocular diseases influence the blood pressure in the anterior vessels. The blood pressure in the anterior ciliary vein is directly related to the intraocular tension. The blood pressure in the anterior ciliary artery was found to be high in cases with scintillating scotoma, optic neuritis, episcleritis, and iritis. The blood pressure is often lower in optic atrophy and pigmentary degeneration of the retina.

Further studies of the choroidal circulation by Stein et al.[6] showed that intravenous injection of sodium nitrate, nicotinic acid, histamine, and ergotoxine had no effect on the choroidal vessels. Epinephrine, however, did cause vasoconstriction. Paul and Leopold[7] conducted similar experiments and found that the usual vasodilators also failed to effect the choroidal vessels. The most efficacious drug to dilate the vessels was not suggested by the authors. Janes and Calkins[8] found that isoflurophate (DFP) caused an enlargement in the diameter of the radial arteries. Homatropine also resulted in enlargement of the vessels, but this was thought to be due to the linear contracture of the vessel.

Congenital Anomalies

De Groot and Freidenwald[9] reported thrombi of the ciliary veins in 10 cases of stillborn infants. The cause or significance was not concluded, but, since this is the first such report, the authors suggest the condition to be a new entity.

Bonaccolto[10] explains at least one cause for coloboma of the lens. Originally, cystic masses are present in the ciliary body which are sufficiently large to interfere with the normal development of the lens. The cysts recede but leave pigment deposits on the posterior surface of the lens and anterior hyaloid.

The inheritance of choroideremia most probably is an intermediate sex-linked dominant, according to Westerlund.[11] Of a series reported, two daughters and two grand-daughters had characteristic fundus changes. Of two brothers with choroideremia, one had a daughter with similar fundus changes but without visual defects.

Inflammation

In contrast to literature of 10 years ago, our present-day articles usually deal with a specific disease of proven etiology with the outline for a specific treatment. The final story has not yet been written, but each year a few cases are separated from the large group of nonspecific uveitis. Once the diagnosis is made, direct attention can be pointed toward a specific treatment. Granted, many articles are still printed on uveitis that offer little more than a review of often-repeated theories, but even some of these are valuable in condensing and crystallizing our previous knowledge.

Sugahara[12] analyzed 110 cases of anterior retinochoroiditis and found the great majority to have been caused by tuberculosis. Such a preponderance may be present in Japan, but elsewhere in the world the large group allotted to tuberculosis has gradually decreased with the improvement of our diagnostic acumen. Davenport[13] calls to our attention that gonorrhea, syphilis, and tuberculosis were the principle causes for uveitis, but venereal disease is relatively uncommon and many uveitis cases attributed to tuberculosis now meet the diagnostic criteria of other specific diseases.

Tuberculosis

The diagnosis of miliary tuberculosis may be difficult, but the presence of choroidal tubercules establishes the diagnosis. Illingworth[14] reported that 75% of children with positive chest x-rays showed choroidal lesions. Histological study of a tuberculoma of the ciliary body showed hyperplasia of the epithelial elements with necrosis of the overlying sclera.[15] Rosselet and Magnenat[16] found that liver biopsies in suspected cases of tuberculous uveitis showed typical tuberculous changes in the liver, even to the point of well-formed tubercles.

Experimental studies in ocular tuberculosis have given considerable help in understanding the mechanism of the disease as well as the effect of newer drugs on the infection. Takahashi[17] injected live tubercle bacilli into the eyes of rabbits and found bacilli in the circulating blood within six hours. Three days after injection, bacteria were recovered from the lungs, liver, and spleen. Five days after injection, the nervous system and lymph nodes were affected. Pascheff,[18] however, injected dead tubercle

bacilli into the subconjunctival tissue near the limbus. After three days nodular lymphocytic infiltration with epitheloid cells appeared in the iris. The author failed to mention whether the rabbits had been previously sensitized or not, but it is presumed that they had been. Live bacilli were injected subconjunctivally into rabbits by Bouzas,[19] and later isoniazid was injected subconjunctivally. The animal progressively improved, and tubercle bacilli were never recovered either by smear or by guinea pig innoculation. Infection failed to develop even if the isoniazid was not injected until 21 days after inoculation with live tubercle bacteria.[20] Miyahara[21] found antibodies in the aqueous one week after injection of tubercle bacilli into rabbits. Administration of corticosteroids impedes the formation of antibodies. The cortiscosteroids are still being tried in the treatment of tuberculous infections of the eye, but, fortunately, Fornaro and Lepri[22] conclude that the use of cortisone in conjunction with antibiotic drugs (streptomycin and isoniazid) in immune allergic rabbits infected with Koch's bacilli failed to result in any favorable modification of the course as compared with the use of antibiotics alone. The same authors[23] did find that the somatotropic hormone (STH) inhibited the inflammatory process and favored a general tendency toward the proliferation of epitheloid cells in the granuloma to the exclusion of necrosis.

There is some disagreement as to the clinical effectiveness of isoniazid. Dolcet-Buxeres[24] reported a case of choroiditis in which new tubercles appeared after treatment with streptomycin but healed after treatment with isoniazid. Gálvez-Montes[25] considers isoniazid combined with streptomycin especially valuable in certain nonallergic types of ocular tuberculosis. The combined treatment of isoniazid, streptomycin, and PAS failed to create any favorable response on a tuberculoma of the iris and ciliary body as described by Milosevic and Blagojevic[26]; however, repeated small doses of x-ray brought about a complete cure. Kopec-Zaleska[27] found that isoniazid improved the general condition but did not effect the ocular infection. A combination of streptomycin and PAS is more effective but still not satisfactory. Blatt et al.[28] finds gold therapy to be useful in diffuse tuberculous choroiditis even in tuberculin-streptomycin resistant cases. Tuberculin is not without danger as a diagnostic skin test. Miller and Smerz[29] reported a case in which bilateral uveitis developed after a tuberculin skin test.

Toxoplasmosis

In spite of the growing importance of toxoplasmosis in ocular disease, relatively few articles were written on the subject this past year. In a careful analysis of 200 uveitis cases effort was made to evaluate tests for toxoplasmosis. Thirty-five per cent of the cases of granulomatous choroiditis were attributed to toxoplasmosis. In those cases where the complement-fixation test was 1:64 or higher, there was 80% correlation between the skin test and dye test. If the 1:16 titers were considered positive, there was no correlation between the two tests. The complement-fixation test is of little value unless it becomes positive during the course of the disease.[30]

Forbes[31] reported 14 cases in which a presumptive diagnosis of toxoplasmosis was made. Treatment of these cases with pyrimethamine (Daraprim) proved successful. The case reported by Deutch and Horsley[32] involves an infant who died of the disease 18 days after birth. Gibson, from the public health department, found that a nearby open garbage dump was the source of infection. Domestic animals often fed from the dump, and it was found that cats, ducks, and dogs were all infected. Mice from the patient's home were also infected. The prevalence of the parasite and the ease with which it can be carried is alarming. However, usual sanitary precautions could eliminate many of the dangers. The use of pyrimethamine appears to be useful in cases with positive-Toxoplasma

fixation test and dye test. Such cases without positive tests did not respond to the drug. According to Perkins et al.,[33] not only is pyrimethamine a good therapeutic agent but its use is a good test for the infection.

Sympathetic Ophthalmia

There is continual interest and evidence toward linking Vogt-Koyanagi-Harada disease with sympathetic ophthalmia. Nishi,[34] in his experiments, sensitized rabbits with egg white. After sensitization, the egg white was introduced into the eye and, at the same time, the area was injured. The injured as well as the fellow eye developed uveitis resembling sympathetic ophthalmia. Dolének [35] feels that sympathetic ophthalmia is an immunotoxic disease in which the antigen may be a microbe joined to deintegrated portions of the intraocular tissue. He reports 70 cases seen in Czech hospitals between 1945 and 1955. Twenty-nine cases followed intraocular surgery. Since the use of cortisone it has been possible to salvage 70% of the cases so treated. Redslob [36] gives a similar explanation by suggesting that sympathetic ophthalmia is due to a saphrophytic organism of unknown nature. When this organism gains access to the eye, it causes a localized focus of infection that later spreads by the blood stream to the other eye. Such a theory is pretty but is not compatible with our present knowledge. The treatment with cortisone has been a great help within recent years. Sturman [37] reported a case so treated, and the sympathizing eye has remained quiescent for two years. By implanting a foreign body or creating a fistularization in the ciliary body, Neidermeier [38] produced a sympathetic inflammation in half of the cases in which tuberculin had previously been given. Cortisone inhibited the response. Sporadic cures of sympathetic ophthalmia by the use of various drugs have been reported. Basile [39] produced a cure with large doses of penicillin. Paez Allende [40] attributes the cure of two cases to the use of cortisone and wide-spectrum antibiotics, but the treatment was not effective until the offending eye had been enucleated.

Ikui and Heyania [41] demonstrated that sympathetic ophthalmia and Harada's disease were identical histologically. Yuge [42] confirmed this work by reporting a case of Vogt-Koyanagi-Harada syndrome and emphasizing the similarity to sympathetic ophthalmia. The author believes that the V-K-H syndrome is sympathetic without known trauma. Unknown trauma to the melanocytes elsewhere in the body could condition the reaction in the oculocutaneous syndromes. It is rare for sympathetic ophthalmia to be accompanied by the complete picture of V-K-H disease. Two cases reported by Fine [43] followed surgery. The presenting symptoms of V-K-H syndrome may be headache and papilledema with simulated increased intracranial pressure; later, uveitis, detached retina, and poliosis developed. Bronstein [44] obtained improvement with prednisone.

Boeck's Sarcoidosis

Ainslie and James [45] found that cortisone was beneficial in the treatment of sarcoidosis if the therapy was begun in an early stage. In a study of 172 cases of Boeck's disease with iridocyclitis, there was strong evidence in favor of tuberculosis as an etiology. Wegner [46] based this conclusion on the histological findings and the frequent presence of Koch bacilli in the Boeck nodules. The evolution of Boeck's disease to tuberculosis and vice versa was frequent and was proved by animal studies. The argument against tubercular origin is the negative tuberculin reaction; however, this may be due to a state of anergy. Cases have been reported in which Boeck's disease has turned into florid tuberculosis after treatment with cortisone. Atypical manifestations of Boeck's sarcoid could not be diagnosed without histological examination. Blatt et al.[47] described a case of an enlarged lacrimal gland which after removal proved to be Boeck's sarcoid. Facial paralysis developed in a

case of uveoparotid fever. The paralysis was relieved by decompression of the facial nerve in the temporal bone. Histologically, the condition proved to be Boeck's sarcoid, as reported by Welson.[48]

It was found by Krannig[49] that the serum titer of antistreptolysin was abnormally high in patients with streptococcal infections. Such a test should be valuable in determining the etiology of some cases of iritis. Further study by Woods[50] showed an effective response from desensitization with Streptococcus vaccine. Some of the failures have responded to an autogeneous vaccine. The vaccines should not be given in mild cases of uveitis that respond to corticosteroids. Drozdowska et al.[51] also found the antistreptolysin titer elevated in many cases of uveal disease, and antirheumatic therapy gave good results in such cases. Alvaro[52] concluded that nongranulomatous uveitis was due to a sensitization to streptococci.

The rheumatic origin of uveitis is an apparent fact, but the uveal inflammation may often precede the joint disease by several years. Hogan et al.[53] thoroughly studied 43 cases with joint disease and associated uveal inflammation. Some of the cases with recurrent iritis failed to show joint disease; however, other laboratory evidence of rheumatic disease was convincing. The acute iritis responds well to treatment, whereas the chronic type does not respond. Still's disease has persistent iritis which resists treatment. Uveitis in acute rheumatic fever occurs rarely, according to Smith[54]; however, uveitis is found in more than 4% of cases of rheumatoid arthritis. Rintelen[55] attempted to classify rheumatic iritis, but his criteria merely suggested a nongranulomatous iritis. In spite of the general opinion that rheumatic fever is associated with uveal disease, Stanworth[56] found no association in a study of 237 cases of uveitis.

In a study of allergic iritis, Walker[57] found the disease to have an acute onset which would clear quickly with antihistamine or cortisone treatment. If the disease is of long standing, convalescence is protracted. Severe uveitis may be caused by the injection of tetanus antitoxin in sensitized patients.[58] The allantoic fluid from chick embryos of more than 13 days caused uveitis in rabbits when injected into the vitreous. The inflammation was transferable when this vitreous was injected intravenously into other rabbits. It was concluded by Yoshida[59] that allantoic fluid of old chick embryos has antigenicity which causes uveitis. Waksman and Bullington[60] found that, by injecting adequate antigen, an Arthus reaction in the form of hemorrhagic uveitis resulted when a homologous antibody was injected intravenously.

Leptospirosis is occasionally associated with iridocyclitis. Doherty[61] found 5 cases of iridocyclitis among 273 patients with leptospirosis. Penicillin in large doses produced more rapid recovery but had no influence on the incidence of uveal inflammation. Oksala and Salminen[62] found the incidence of uveitis in leptospirosis to be much higher than did Doherty. A thoroughly proved case of leptospirosis with uveitis was reported by Bruntse.[63]

A number of papers reported rare systemic infections complicated by uveitis. Central choroidosis caused by amebiasis is sufficiently common to include in a differential diagnosis of central retinal lesions. Braley and Hamilton[64] feel that early diagnosis is important, since corticosteroids are definitely contraindicated in amebic infection.

Brown et al.[65] observed a case of juxtapapillary choroiditis associated with pulmonary coccidiodomycosis. The ocular lesion subsided after lobectomy. Holland and Worlton[66] reported for the first time a pleuropneumonia-like organism that caused a nongranulomatous uveitis. The focus of infection was found to be in the prostate. Oxytetracycline cleared both the focus and the uveitis. D'Ermo[67] suggested that the rare iridocyclitis seen in multiple sclerosis is due to the sensitivity of the uvea to the virus of multiple sclerosis. Laboratory tests

establishing the virus and relationship to the uvea were not recorded. Temporal arteritis was associated with iritis, and Lindblad [68] affected a cure by arterectomy. Obliterative arterial changes in the retina may produce a hypopyon uveitis. Müller [69] reported no evidence of systemic disease in his two cases, but the pathologic changes in the eye suggested periarteritis nodosa. In spite of many works to the contrary, Ullerich [70] recommended the use of corticosteroids for the treatment of granulomatous uveitis. The consensus is that corticosteroids are contraindicated except in sarcoid and sympathetic ophthalmia. King et al.,[71] in an effort to evaluate various corticosteroids, found that prednisone was twice as potent as intramuscularly administrated cortisone but less potent than hydrocortisone. Leopold et al.[72] found that local applications of prednisone and prednisolone penetrated less easily than cortisone or hydrocortisone. Systemic administration showed the reverse to be true.

In a discussion on the treatment of uveitis, Neilson and Kirby [73] emphasized the advancement of our knowledge as regards the etiology and mechanisms causing uveitis. Fortified by such knowledge, our treatment is more direct. New drugs for the treatment of tuberculous uveitis, such as isoniazid, have been encouraging. The combined use of steroids is a new trend. Nonspecific treatment has been simplified somewhat by the use of steroids, but otherwise little change has been made. The universal use of fever has declined, but occasionally fever is used with advantage when steroids are not effective. Apparently side-responses, which are more or less unknown, prove beneficial. Chronic uveitis found in women who have passed the age of fertility might be due to hyperfolliculinism as revealed by the urinary output of sexual hormones and 17-ketosteroids and by the Papanicolaou technique.[74] Ruiz-Barranco [75] suggests two forms of uveitis. One is a syndrome of neurogenic origin, which responds to the usual nonspecific treatment. The other is an intrinsic disease of the uveal tract. Various treatments, such as mechlorethamine (nitrogen mustard), succinic acid, and Irgapyrine with phenylbutazone (Butazolidin) gave excellent results. However, nitrogen mustard has its risks. Experimental use of vitamin D in large doses proved beneficial in chronic uveitis. Remky [76] believes that vitamin D causes reduction in the permeability of the blood-aqueous barrier as well as an antiparasympathetic action.

Increased intraocular tension is thought by Weekers et al.[77] to be caused by the increased resistance of the aqueous outflow. Reduction of this resistance may be obtained by the use of atropine and cortisone. Failure of such treatment may be controlled by the use of epinephrine and acetazolamide (Diamox) in an effort to reduce the formation of aqueous. François and Neetens [78] reported two cases of ocular hypertension appearing during the course of herpes zoster and preceding iridocylitis. This was not a congestive glaucoma, and the angle was open. Epinephrine caused a decrease in the intraocular tension.

Brockhurst et al.[79] stressed the importance of gonioscopy in studying a suspected case of uveitis. Mutton-fat deposits may be present in the angle even if the slit-lamp examination is negative. Such an early sign may be valuabe in the detection of sympathetic ophthalmia. Lokshin [80] suggests that if a patient with suspected uveitis lowers his head for two to three minutes a hidden exudate will appear in the anterior chamber. Of 185 patients studied with uveitis, 153 had normal sinus x-rays. It was therefore concluded by Edling [81] that sinusitis was of little importance as a focus of infection causing uveitis. However, he did say that sinus infection may contribute toward the chronic nature of the disease. On rare occasions Offret et al.[82] found bacteria in the aqueous of uveitis which were the same as those found in the discharge from infected tonsils. Tonsillectomy caused the eye to clear. Postoperative iridocyclitis after cataract extraction may be due to normal reac-

tion to trauma. However, foreign material in the wound or presence of cortex in the anterior chamber in a sensitized eye may cause iridocyclitis. Persistent inflammation is an indication to explore the wound thoroughly, according to Hogan.[83]

Degenerative Changes

During the past year several reports were made concerning Fuchs' syndrome, or heterochromia with iris atrophy. Georgiade[84] reviewed the literature and discussed 58 cases with characteristic findings. He believes that the pathogenesis is the result of vascular disorders of the neurovegetative centers. The vasomotor and thalamic centers are of major importance. He feels that the hypochromia is due to vascular lesions and not to a decrease in iris pigmentation. The proof of these conclusions is not clear to me. Dhanda[85] supports the noninflammatory character of Fuchs' disease by reporting two cases in which heterochromia developed without there ever being signs of inflammation. Further study of the disease was done by Miglior,[86] who examined the aqueous for pH, glucose, lactic acid, and protein. The protein content was elevated, but the other findings were within normal values. Aniridia associated with iris atrophy has been reported by MacDiarmid.[87]

Two cases were reported in which Descemet's membrane was present on the anterior surface of the iris. Monschut[88] found this condition in eyes that had been injured many years previously. Such a condition is not uncommon in chronic glaucomatous eyes with iris atrophy. Rehák[89] wrote a whole paper on the report of two cases with rubeosis iridis diabetica, where he concludes that the rubeosis of the iris is due to a general disease of the ocular vessels. Glaucoma probably results from the vascular changes in the eye. François and Neetens,[90] however, reported three cases of spontaneous regression of rubeosis iridis. The glaucoma was due to the neovascularization of the angle, resulting in decreased aqueous outflow. With the disappearance of the neovascularization the tension became normal.

A spontaneous detachment of the choroid developed after gold therapy. Bed rest or trephination was not successful in obtaining a cure.[91] The methods of establishing a clinical diagnosis were not discussed. Krasnov and Shoulpina[92] believe that 60% of all cases following trephine operation develop choroidal detachment. The cause is thought to be due to a transudate from the choroidal vessels. Treatment is perforating diathermy over the involved area.

Maumenee[93] discussed the hypersensitive reaction of collagen diseases as it affects the uvea. Lupus erythematosus, periarteritis nodosa, dermatomyositis, and rheumatoid arthritis are among the diseases discussed. Boeck[94] reported a case of periarteritis nodosa associated with herpes zoster and therefore suggested a viral origin, but there is little evidence to support such a theory.

Grönblad-Strandberg syndrome is a part of a generalized disturbance of elastic tissue. The syndromes may not be complete. After treatment with isoniazid blue striae appeared in the skin.[95] Kuběna and Bartosova[96] believe the disease to be a disease of systemic inferiority of the mesenchyme manifesting itself by an increased capillary permeability, bleeding, and transudation.

Hemorrhages and macular edema may be caused by high-voltage electric shock. Jonquères[97] does not believe that these changes are the result of the spark. Baum,[98] in his experimental application of ultrasonic radiation to rabbit eyes, found that various changes in the iris and ciliary body were produced if the length and intensity of the exposure was sufficient. Dispersion of pigment, synechiae, and cellular inflammation were characteristic. Transplantation of the inferior oblique may improve the choroidal circulation. Burnside[99] suggests such a treatment for senile macular degeneration.

Epithelial cysts of the iris are relatively rare unless there is a definite history of perforation. Guerry and Wiesinger[100] reported a translucent cyst of the iris stroma.

Histologically, the cyst was lined with cuboidal cells that were covered with a cuticular membrane. The exact cause of the cyst was unclear. Santoro,[101] however, reported a cyst of the iris that developed 32 years after a corneoscleral wound. Surgical excision followed by diathermy was successful. The spontaneous iris cyst of Kozakiewicz [102] appeared to float freely in the anterior chamber. The cyst was removed through a corneoscleral incision. Its origin was thought to be from the pigment seam. However, the histologic description identified the presence of connective tissue and branching pigment cells. Such cells most probably come from the stroma.

A malignant melanoma of the iris occurring in a 15-year-old boy was reported by Rosenberg.[103] The eye was not enucleated until eight years after the lesion was noted, in spite of change in size and glaucoma. Radioactive phosphorus or biopsy might have aided in earlier diagnosis. Law and Hansell [104] have followed iris tumors by photographs with fixed magnification. If superimposition of the negatives showed increase in size, surgical removal was carried out.

In a well-documented case of leiomyoma of the iris Brown et al.[105] found radioactive phosphorus uptake to be negative. This may suggest the benignity of the lesion. Pinkerton [106] described a case of leiomyoma arising from the dilator fibers of the iris. Neurinomata are even less common than leiomyomata, and the histological picture is similar. However, Böke [107] can differentiate the two by special stains.

Malignant melanoma of the choroid comprises the great majority of tumors involving the choroid. For the most part, the literature is made up of case reports having interesting features. Maybe the report of such observations will contribute toward solving the mystery of melanomas of the choroid. The different manners in which these tumors act strongly suggest the fact that we are dealing with not one tumor but several, all with the common characteristic of pigment. The great difference in the malignancy helps to confirm this idea. Cortés [108] reported a case of malignant melanoma which showed extrabulbar extension at the time of enucleation. The contiguous orbital tissue was treated with diathermy and later treated with radium. The value of such treatment is questionable, since 30-year follow-up of such cases treated by enucleation alone has been observed. Schiff-Wertheimer and Loisillier [109] report a case in which a patient developed a melanoma in one eye and later the fellow eye was found to have sympathetic ophthalmia. No mention was made as to whether the tumor was necrotic or not; however, the inflamed eye was cured with cortisone. In a series of 228 eyes with malignant melanoma of the choroid, Kirk and Petty [110] found that 10% had been enucleated without the presence of a tumor having been suspected. Oddly enough, there were 81 additional eyes in which tumor was diagnosed but in which none was found pathologically. Badtke [111] also reported a series of 11 cases in which eyes were enucleated for melanoma and no tumor was found. Subretinal hemorrhage, choroiditis, hemangioma, tuberculoma, and diffuse melanosis were the conditions found instead of melanoma. Blanco and Plantoni [112] discuss mistaken diagnosis involving melanomas of the choroid. They report a case of choroidal hemorrhage and suggest that such a mistake is unavoidable. However, there is no mention of the use of radioactive phosphorus as an aid in such cases. Ham [113] states that slit-lamp examination of the fundus can often confirm the diagnosis of malignant melanoma. The report of a choroidal cyst by Hruby [114] emphasizes the similarity to malignant melanoma. Such a lesion is said to be difficult to differentiate from melanoma. Such a cyst should show an increase in rather than an interference with transillumination. P^{32} might also be helpful. Friede [115] made a rather brave attempt to remove a melanoma of the ciliary body locally. Sections of the specimen removed

suggested that the whole tumor had not been completely excised. Subsequent enucleation and study showed no evidence of tumor remaining in the globe. Inflammation has been accused of causing the development of melanomas in the choroid. Hoffmann [116] reported three cases where long-standing inflammation existed prior to the development of a melanoma. On rare occasions melanomata are associated with other primary tumors elsewhere in the body. Nover [117] recorded three such cases.

Recurrent hemorrhages in the choroid may simulate a tumor. A case of a 10-year-old boy was reported by Cucco,[118] in which histological sections confirmed the diagnosis of hemorrhage.

Boulanger [119] considers metastatic tumors of the choroid to be rare. This is true in eye hospitals, but these tumors are not so rare as they are thought to be when cases are followed into chronic disease hospitals.

Clinical recognition of hemangioma is extremely difficult because there are no clear characteristic signs. Goreis [120] reported five cases of hemangioma of the choroid and diagnosed one clinically. This case was a 13-year-old girl with several hemangiomas of the skin. No specific diagnostic signs are offered.

The recent use of radioactive phosphorus in the detection of intraocular tumors is a valuable addition to our armamentarium for diagnosis. O'Rourke et al.[121] studied the differential uptake of P^{32} in ocular tissue and found that enough P^{32} enters the globe to assure accurate counting under clinical conditions. The surrounding structures do not attract sufficient P^{32} to obscure emissions arising from within the globe. Ocular inflammation causes an increased P^{32} uptake but less than with intraocular tumors. Dunphy et al.[122] carefully reviewed 31 cases of suspected intraocular malignancy. Twenty-one were proved to be malignant by pathologic examination. Fifteen were so situated as to be accessible to the Geiger counter. All of these were positive. The remaining six proved cases that gave a negative result had tumors located far posteriorly. A reading of less than 30% over the normal was considered negative. One false-positive reading was due to a disciform degeneration, but this was a clinically benign case. In his Charles H. May lecture, Dunphy [122] listed the following three limitations to the test: 1. A posteriorly placed lesion out of range of the counter may give a false-negative reading. 2. If the counter is placed over the recti muscles, especially the medial rectus, the reading may be abnormally high. 3. A positive reading taken immediately after injection is unreliable, whereas the 24-hour reading is far more reliable. Donn and McTigue [124] confirmed Dunphy's findings. However, they found that patients treated with diathermy showed positive results for at least one month after treatment. Shapiro [125] suggests the potential danger of body irradiation and cautions that the test should be used only in indicated cases.

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Case Reports

Cicatricial Ectropion Caused by Cutaneous Blastomycosis

FREDERICK C. BLODI, M.D., and WILLIAM C. HUFFMAN, M.D., Iowa City

This case is being reported in order to illustrate the effects of cutaneous blastomycosis on the lids and its aftereffects when the infection has been controlled with modern fungicidal therapy. This report should further serve to reemphasize the important basic factors which should be employed in the reconstruction of a severe cicatricial ectropion with skin grafts.

Report of Case

A 57-year-old white man was first admitted to this hospital in April, 1953. He gave a history of having been affected with cutaneous blastomycosis since 1937. He had been hospitalized on numerous occasions for this condition, and the diagnosis was established by repeated bacteriologic and histologic examinations. Numerous attempts with iodine treatment had resulted in an intolerance to therapeutic doses of iodide but not in an arrest of the disease.

The past history revealed pulmonary tuberculosis, arrested since 1936, and a duodenal ulcer diagnosed in 1950.

The entire skin of the face and the neck was involved on admission. There were numerous red ulcerated lesions with heaped-up granulation tissue at the borders. The largest lesion was over the right maxilla, and another one was beneath the left external naris. Between these areas of active inflammation were white flat scars scattered mainly over the forehead, the cheeks, and the neck. All the lids were thickened and everted. The tarsal conjunctiva was reddened. The patient could close his lids with difficulty. The eyes were normal (Fig. 1).

Fig. 1.—Active blastomycosis involving the lids.

Direct smears from the active skin lesions of the face showed refractile budding organisms. Cultures and biopsy confirmed the diagnosis of blastomycosis. No systemic involvement was found.

The patient was treated with stilbamidine isethionate. He received 150 mg. in 200 cc. isotonic saline intravenously every day for a total of 37 injections, or 5.55 gm. The skin lesions healed promptly, and all active foci were replaced by scar tissue. The patient developed some numbness over the upper lip, the nose, and the lower midforehead, but no other toxic manifestations of the drug became evident.

The patient was readmitted one year later for a plastic repair of the cicatricial ectro-

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From the Veterans' Administration Hospital, Iowa City, and the Departments of Ophthalmology and Otolaryngology, State University of Iowa College of Medicine.

Fig. 2.—*A*, cicatricial ectropion of all four lids. *B*, close view of the left eye.

pion of all four lids (Fig. 2). The lids could not be closed sufficiently to cover the cornea because of the dense scar tissue in the face. The tarsal conjunctiva was exposed on all lids, and the patient suffered from tearing and chronic conjunctivitis. The skin of the face and the neck showed loss of pigmentation and atrophy. The ears were involved in that process, but no active skin lesions were present.

The plastic repair was done in four stages. The upper lids were reconstructed separately (March 23, 1954, and April 20, 1954) but in the same way. With use of general anesthesia a knife incision was made 2 mm. away from the lid margin, following the latter from the inner canthus to the outer canthus. The skin of the upper lid was then mobilized to such an extent that the tarsus could be placed on the lower lid, touching the lower lid margin without stretching. Mobilization was continued until the defect seemed to be overcorrected. The lower edge of the upper lid could actually be drawn down to the lower orbital margin (Fig. 3). All hemorrhages were stopped with hemostats and sutures. The split-skin graft was

Fig. 3.—Mobilization of the upper lid. The overcorrection becomes apparent.

Fig. 4.—The skin graft is in place and sutured to the bed.

then taken from the inner side of an upper arm. It was taken with an electric dermatome at a thickness of 10/1000 in. Two lid adhesions were placed. The graft was sutured to the surrounding skin with numerous 0000 nonabsorbable surgical (silk) sutures (Fig. 4). The sutures were left long and tied over moist sponges, which were put tightly on the graft. A pressure bandage was applied, and the patient was given pencillin. The bandage was changed on the eighth day, and the sutures were removed.

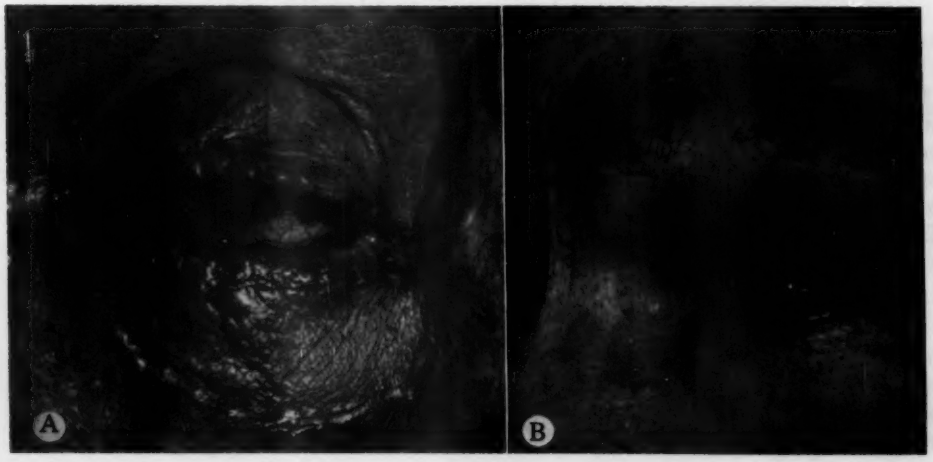
The lower lids were also repaired separately (May 6, 1954, and June 16, 1954). A knife incision was made along the lower lid margin from the inner to the outer canthus. The skin of the lower lid was then mobilized in such a fashion that the tarsus was freely movable and could be placed on the upper lid without stretch. It was found that the lid margin was now too long, and a small piece had to be excised so it would lie against the globe better. The margin was reconstructed by the halving procedure, and lid adhesions were done. A full-thickness skin graft was then taken from the supraclavicular area. The graft was freed from all adhering fat tissue. It was anchored to the prepared bed by numerous 000000 and 0000 silk sutures. The latter were left long and tied over moist sponges. A pressure bandage was applied, and the patient was given penicillin. The dressing was changed on the 10th day, and the sutures were removed.

All the grafts took without any complication. The lids returned to normal position, and the patient was well pleased about the final appearance of his face. The appearance of the eyes during the various stages of repair and one year following the last operation is illustrated in Figure 5.

Comment

We wish to reemphasize the fact that a thin split-thickness graft is the method of choice for correcting a cicatricial ectropion of the upper lid. The skin should be taken from the inner aspect of the upper arm if skin from the other upper lid is not available. Because of the marked tendency of this graft to shrink, overcorrection is mandatory. The upper lid has to be mobilized in such a way that the lid border reaches the lower orbital margin. Lid adhesions are then of less importance or unnecessary. The graft is applied by the "epithelial outlay graft" technique, in which the edge of the graft is sutured to the wound with numerous silk sutures. The sutures are left long and tied over a ball of moist gauze to insure even and continuous pressure. The dressing

Fig. 5.—*A*, the right eye one year after operation. *B*, the left eye one year after operation.



should not be disturbed for 10 to 14 days. This method has been successfully used in burns to the lids.[1,2]

In order to repair a cicatricial ectropion of the lower lids a full-thickness graft can be used, as the weight and lack of suppleness are here of less importance than in the upper lid. The skin should be taken from an upper lid if possible. This was impossible in our case, and the retroauricular area was also not available. We therefore used skin from the supraclavicular area. Overcorrection should again be the goal, though a full-thickness graft will have less tendency to shrink.

Summary

A patient with cutaneous blastomycosis involving all four lids is reported. The infection was controlled with stilbamidine.

For repair of cicatricial ectropion of the upper lid a split-thickness skin graft from the inner aspect of the upper arm should be used if skin from the other upper lid is not available. Overcorrection is mandatory, and the "epithelial outlay graft" technique is advised.

For repair of cicatricial ectropion of the lower lid a full-thickness skin graft from an upper lid, the retroauricular area, or the supraclavicular area should be used, in this order of preference. Overcorrection is here also indicated, though less contraction of the graft can be expected than in the split-thickness graft.

Department of Ophthalmology, University Hospitals.

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Congenital Paralysis of Lateral Conjugate Gaze

Occurrence in a Case of Klippel-Feil Syndrome

S. H. WITZEL, M.D., Toronto

Several of the reported cases of Klippel-Feil deformity have exhibited a variety of squints. The following case is reported because of the unusual ocular findings.

The patient, a white boy born in 1949, was first seen in the eye clinic in 1952 because his parents thought he had a squint. At that time no squint was noted. However, because of poor cooperation excursions were not tested. Retinoscopy showed O. D.+ 1.75 sph; O. S. +2.00 sph. The fundi were normal.

The child was noted to have a cleft palate, flat feet with lengthening of the longitudinal arch and slight valgus of the heels, and a typical Klippel-Feil deformity of the neck. X-rays revealed poor segmentation of the cervical spine with fusion of both the vertebral bodies and spinous processes and hemivertebrae. Spina bifida occulta of the upper two dorsal vertebrae was present. There was no family history of strabismus or neurological or skeletal abnormality.

On a return visit in 1953 it was noted that, while vertical movements were intact, the patient could not turn his eyes to either side. The other ocular findings were unchanged. The cleft palate had been repaired.

In April, 1957, he returned to the clinic. The findings were as follows: total paralysis of conjugate gaze movements to the right and to the left, not only to command movements but also on bringing objects of interest into his field of vision and on the patient's attempting to follow objects. There were no random movements from side to side. Since the boy's neck was immobile, it was necessary for the patient to rotate his trunk at the waist in order to look sideways. Rapid passive rotation of the trunk in either direction failed to elicit any ocular deviation. There was no limitation of vertical movements. The near point of convergence (N. P. C.) was 20 cm., and slight but definite convergence movement could be observed. On the synoptophore the following measurements were recorded: S. M. P. present, orthophoria, adducts +7 degrees with fusion slides, stereopsis present.

The pupils were round and equal and reacted to light and in accommodation. The fundi were normal, as were the visual fields. Uncorrected visual acuity was 20/25 in each eye.

The child appeared bright, generally well, and happy. His parents stated that he was consistently at the top of his class at school. General examination revealed complete nerve deafness on the left, but there was no facial weakness or other neurological anomaly.

Cold caloric tests were done to assess vestibular function. Stimulation of the left ear for 30 seconds with water at 48 F elicited no eye movements of any kind with the head in any position. Similar stimulation of the right ear produced only a regular rotatory nystagmus with the fast phase counter-clockwise, which persisted for 2 minutes 10 seconds.

Comment

The absence of vestibular movements and random movements clearly indicates a true gaze palsy rather than a case of congenital ocular aproxia of the type described by

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From the Departments of Ophthalmology, University of Toronto and Hospital for Sick Children.

Cogan.[1] Of the various classifications of conjugate gaze palsies, that of Kestenbaum [2] has the advantage of simplicity. He divides horizontal conjugate palsies into four main groups.

1. All forms of conjugate gaze movements except vestibular are affected (Bielchowsky type).

2. Preservation of following movements and vestibular movements (Oppenheim-Roth-Uhthoff type).

3. Disturbance of all command, optically elicited, follow, and vestibular movements, i. e., all forms of lateral conjugate movement (Bertelsen-Roenne and Luettge type).

4. Disturbance limited to command movements with preservation of all the other forms (Kestenbaum-Stenvers type).

The large majority of all gaze palsies are on an acquired basis. It is to be noted that our case is a congenital example of the third type.

Congenital conjugate gaze palsies are rare. Dupuy-Dutemps [3] described one such case in an 8-year-old girl who had paralysis of conjugate lateral gaze with the preservation of convergence. However, his case differs from that reported here in that a right facial paralysis was present and the child had no fusion.

To Bauman [4] must go the credit for the first description of the mirror movements of the hands that are occasionally seen in patients with Klippel-Feil syndrome. In reporting six new cases of this syndrome he included that of a boy of 4 years who "could not turn either eye outward." He made no mention of a facial paralysis. Since this was the only reference to the eyes in the report, one cannot judge whether his case had a bilateral abducens paralysis or was similar to this case. With the possible exception of Bauman's patient, to our knowledge this case is the first reported exhibiting as a congenital lesion a total paralysis of conjugate lateral gaze to both directions with preservation of convergence, with fusion, and with an absence of involvement of nearby structures such as the facial nucleus or the pyramidal tract.

The chief interest of the case is that it would appear to be good clinical evidence for the existence of a subcortical center for conjugate lateral gaze movements. According to Cogan,[5] it is not known whether this center is a separate nucleus near the abducens or is actually a portion of the vestibular nucleus. Wherever its exact location, all the ocular findings in this case can best be explained by a bilateral aplasia or a destruction of this pontine center for lateral gaze.

Summary

A case of congenital complete paralysis of horizontal conjugate gaze to both sides in a patient with Klippel-Feil deformity of the neck is presented. There was no strabismus; there was Grade III fusion, and movements of adduction on convergence were preserved. Apart from deafness of the left ear no other neurological abnormalities were present.

Similar cases are rare.

The findings in this case may be considered evidence for the existence of a center of conjugate lateral movements.

Dr. A. Lloyd Morgan, Ophthalmologist in Chief, Hospital for Sick Children, Toronto, gave permission to present this case.

Department of Ophthalmology, Banting Institute, University of Toronto (5).

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An Effective Portable Animal Platform for Zeiss Opton Slit Lamp Examinations

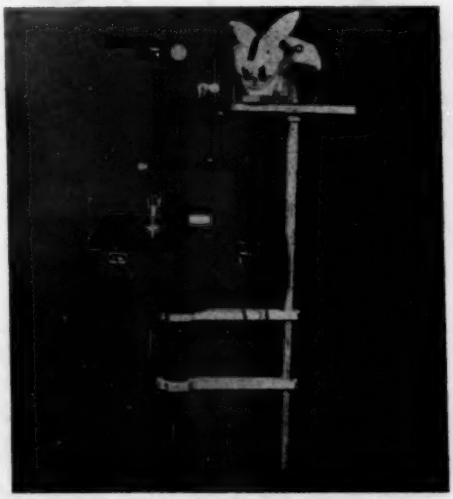
ARNOLD A. SWANSON, M.S.; HEINRICH W. ROSE, M.D., and JACK I. TAUBE, M.D., Randolph Field, Texas

Difficulties in positioning rabbits for eye examinations have led to the development of an adjustable swivel-type platform which can be mounted directly on the stand of a Zeiss Opton Slit Lamp.

The platform consists of ¾ in. thick hardwood measuring 18 by 12 in. A flange, 4½ in. in diameter fastened by screws, is positioned off center on the undersurface of the platform. This, in turn, is supported by aluminum tubing 1¼ in. in diameter and approximately 35 in. long inserted into the flange. This tube is held in position by two connecting-rod-type stem clamps measuring 14 in. fastened to the central support of the Zeiss stand. With the aid of Allen screws in these clamps, upward and downward adjustments can be made in addition to the usual slit-lamp adjustments. A picture of the platform mounted on the Zeiss stand is shown.

Monkeys may also be examined with this platform when they are tied in the prone position with the head hyperextended and held firmly.

Any suitable head stockade type of box is satisfactory for rabbits that will hold the head in position and maintain the animal in a quiet state for examining purposes.



Received for publication June 21, 1957.

U. S. A. F. School of Aviation Medicine, Randolph Air Force Base.

A New Contact Lens for Recording the ERG in Rabbits

BENJAMIN ZIV, M.D., Providence, R. I.

Electroretinography (ERG) is well known as an aid in establishing diagnosis in several eye diseases and in serving as a tool for pure research. Response, of course, depends on such variables as light source (stimulus), apparatus, size of the pupil, and location of the area of retina which is stimulated; it is also important that records be obtained under constant standard conditions.

The purpose of this paper is to describe a contact lens for use in recording the ERG in rabbits (Fig. 1). The contact lens developed by Riggs in 1941 made it possible to record the ERG in human beings without discomfort. The present contact lens is a modification of the original (Fig. 1*C*), which, as used with human beings, was equipped with an electrode (*E*) identical to that shown in Figure 1. This electrode consists of a silver disc cemented into a hole in the contact lens. The surface of the disc is either flush with the inside surface of the lens or slightly recessed in order to prevent direct contact of the silver with the cornea. The edges of this hole are carefully beveled so that the entire inner surface is smooth, and a stiff brass wire covered with beeswax is soldered to the silver disc. A fine flexible wire connects the electrode with a binding post for the input lead to the amplifier.

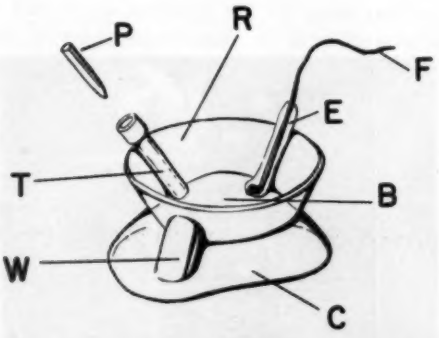


Fig. 1.—New contact lens for recording the ERG in rabbits, left eye (for the right eye *E* and *W* are reversed as in a mirror image). *C*, contact lens covering the eye. *T*, tube for filling lens with fluid. *E*, electrode made of pure silver wire coated with cement and beeswax. *P*, plug for tube. *W*, plastic wedge fitting inside the nasal canthus to prevent rotation of the contact lens. *R*, rim used to prevent closure of lids. *F*, flexible enameled copper wire leading to amplifier. *B*, corneal bulge of contact lens through which light enters the eye.

Additions to the contact lens make it suitable for use with rabbits, the principal change being the addition of a large plastic flange surrounding the corneal bulge of the contact lens. This flange consists of the outer rim (*R*) of a second contact lens. This rim is obtained by cutting out the corneal portion of a regular contact lens so that the rim fits tightly around the corneal bulge of the contact lens (*C*). The purpose of this rim is to prevent closure of the lids and to insure a clear opening (*B*) for light to enter the eye at all times.

Two other features have been added to the original contact lens. The first consists of a triangular wedge of plastic material (*W*) cemented between the two main elements (*C*) and (*R*). This wedge fits into the nasal canthus of the rabbit's eye, thus preventing rotation of the lens. The second feature consists of a tube (*T*) which passes through the lens (*C*) in order to permit the injection of isotonic contact fluid. After being filled with fluid, the tube is closed by a small plastic plug (*P*); this minimizes the occurrence of air bubbles in the fluid. With this contact lens the cornea remains clear, and ophthalmoscopy of the eye is possible even after numerous experiments with the same animal.

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Paper 51, Retina Foundation.

Research Fellow of the Retina Foundation, Boston.

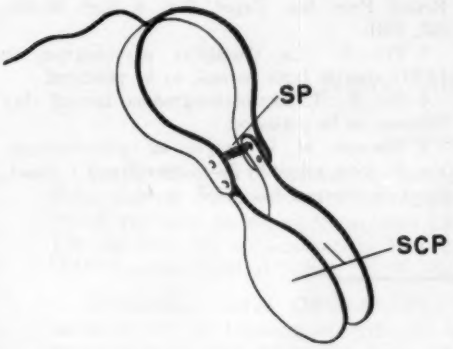

Fig. 2.—New grounding electrode. *SP*, spring. *SCP*, silver contact plate.

An improved ground electrode, large and flat in appearance, has also been developed for the rabbit. This device consists of a double spring-supported silver electrode (Fig. 2) which is placed over the ear of the animal so that it makes contact on each side (Fig. 3). Conventional saline electrode paste is used. Muscle artifacts and contact instability are minimized with this device. The animal is kept in an especially built cage, which greatly restricts its movements (Fig. 4).

Development of appropriate apparatus obviously is desirable but is no guarantee of dependable results. In addition, the physiological variability of the animal must be considered. Only after determining the upper and lower limits of the normal response of the retina is it possible to distinguish responses outside the normal range. A paper describing variations of the ERG and the upper and lower limits in normal rabbits is to be published.[3]

Summary

A new contact lens has been developed for use with rabbits which offers the following advantages: 1. The lids are prevented from closing; thus the rabbit maintains clear vision at all times. 2. Rotation of the lens is prevented, and so electrical contact remains constant. 3. Air bubbles are minimized. 4. The cornea stays clear for ophthalmoscopy even after numerous recordings.

A new grounding ear-electrode is also shown, and attention is called to the problem of physiological response variability within a single animal and from one animal to another.

This work was done under the guidance of Prof. Lorrin A. Riggs, Psychology Department, Brown University, Providence, R. I.

Retina Foundation, 30 Chambers St., Boston 14.

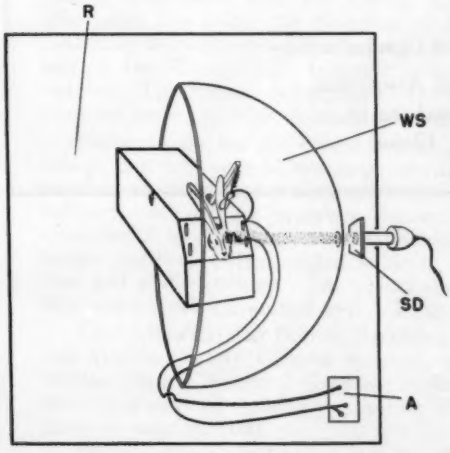

Fig. 3.—Animal in the recording cage. *R*, recording cage. *WS*, white surround. *A*, amplifier input leads. *SD*, strobe lamp diffusing plate.

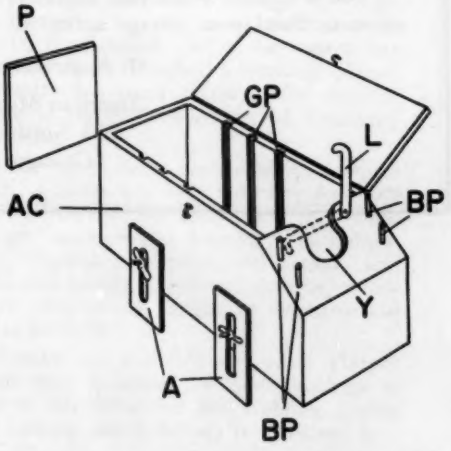

Fig. 4.—Animal Cage. *AC*, animal cage. *BP*, binding posts. *Y*, yoke. *L*, latch to hold head in position. *GP*, grooves for partition. *P*, movable partition. *A*, adjustible legs.

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Correction

In the article "Coat's Disease," by Dr. George N. Wise, in the November, 1957, issue of the Archives the cuts of Figures 6 and 7 (page 740) were accidentally interchanged; the legend for Figure 6 applies to the illustration labeled Figure 7, and vice versa.

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News and Comment

ANNOUNCEMENTS

Delta Gamma Foundation Scholarships.—Scholarships are offered by Delta Gamma Foundation for the training of (1) orthoptic technicians, (2) teachers of partially seeing children, and (3) specialists for blind preschool children. The deadline for applications is May 1, 1958. For further information write to Delta Gamma Central Office, 50 W. Broad St., Columbus 15, Ohio.

Orthoptic Course Offered.—The Kresge Eye Institute again offers its facilities for the training of orthoptic technicians. This program is open to any young woman over 20 years of age who has successfully completed at least two years of college or is a graduate nurse. Good health and vision are required of the trainees.

The course consists of 12 months' didactic and practical training. Didactic training, which is part of the basic ophthalmology course for doctors at Wayne University Graduate College of Medicine, will be given five mornings a week for the first semester. Lectures on refraction, retinoscopy, physiological optics, perimetry, ocular anatomy, neuroanatomy, and motility are given by members of the Kresge Eye Institute staff and professors of Wayne State University College of Medicine.

Practical training must begin in mid-August, one month prior to the beginning of the lecture courses. This practical training continues for one year, at which time students are eligible to take the board examinations for certification given by the American Orthoptic Council orally in August and in writing each fall.

Limited financial assistance is available for some students who require it. Requests may be made either through Kresge Eye Institute or the Delta Gamma Fraternity (Mrs. H. L. Marchant, 4006 Vergilia, Chevy Chase 15, Md.). For further information write to A. D. Ruedemann, M.D., Kresge Eye Institute, 690 Mullett St., Detroit 26.

Courses in Basic Ophthalmology.—A comprehensive course in basic ophthalmology is offered by Wayne State University Graduate College of Medicine in cooperation with the Kresge Eye Institute. Set up in its present form nine years ago under the direction of A. D. Ruedemann, M.D., the course has constantly been improved and expanded. A new auditorium and a teaching laboratory at the Kresge Eye Institute have greatly improved facilities for didactic training. The roomy well-equipped eye clinic in the Farwell Annex of Receiving Hospital makes possible thorough clinical training.

Prerequisites for the course are an M.D. degree from an accredited medical college and one year of rotating internship. Classes are held full-time for nine months; six mornings a week are taken up by lectures; five afternoons, by clinics. Subjects covered are anatomy, bacteriology, embryology, histology, pathology, ophthalmic biochemistry, ophthalmoscopy, physiologic optics, refraction, and ocular motility. Other related subjects are also briefly surveyed, such as, nutrition and endocrinology. The principles of surgery are taught by lectures and laboratory work on animal eyes. Tuition is $300.00.

Five fellowships at Detroit Receiving Hospital are available each year. Harper and Wayne County General hospitals send their residents in ophthalmology to Wayne State University Graduate College of Medicine for this training during their first year of residency. Tuition for fellows and residents in affiliated hospitals is only $100.00.

Openings are available for the academic year 1958-1959. Classes begin on Sept. 8, 1958. Further information may be obtained from A. D. Ruedemann, M.D., 690 Mullett St., Detroit 26.

Seminar on Glaucoma.—A Seminar on Glaucoma with particular emphasis on gonioscopy and the study of the anterior angle will be given at the Brooklyn Eye and Ear Hospital on May 19, 20, and 21, 1958. Ample opportunity for practical instruction in the use of the gonioprism will be given, and material from the glaucoma clinic will be utilized. The Course will be given by Dr. Daniel Kravitz, assisted by Drs. Mortimer A. Lasky, A. Benedict Rizzuti, Abner S. Rosenberg, Nicholas P. Tantillo, and Samuel Zane. Registration is limited to six ophthalmologists only. Registration and the fee of $50 may be addressed to Dr. Daniel Kravitz, Brooklyn Eye and Ear Hospital, 29 Greene Ave., Brooklyn 38.

Department of Ophthalmology, St. Louis University School of Medicine Scientific Program.—A one-day scientific program will be presented the St. Louis University School of Medicine Department of Ophthalmology in honor of the twenty-fifth anniversary of its main teaching hospital, Firmin Desloge Hospital, Thursday, March 27. Ophthalmologists throughout the country are invited to attend the program free of charge. Guest speakers and their subjects will include Dr. Bernard Becker, professor of ophthalmology, Washington University, "The Role of Electrotonography in the Management of Glaucoma"; Dr. V. Everett Kinsey, assistant director of research, Kresge Eye Institute, Detroit, "Lens Metabolism in Normal and Diabetic Animals"; Dr. Paul A. Chandler, associate professor of clinical ophthalmology, Harvard University, "Practical Considerations in the Management of Narrow Angle Glaucoma," and Dr. Elmer J. Ballantine, senior instructor in ophthalmology, department of surgery, Western Reserve University, who will be the guest speaker at the evening dinner meeting of the St. Louis Ophthalmological Society, which will conclude the session. A fifth guest speaker is to be announced. Luncheon at Desloge Hospital will be provided free of charge. Send reservations to Dr. William H. Vogt Jr., Chairman, Desloge Jubilee Committee, 1325 S. Grand, St. Louis 4.

GENERAL NEWS

Medical Research Foundation Established for Tay-Sachs' Disease and Allied Disorders.—A new nonprofit foundation has been established to support and stimulate research, clinical, and educational programs in Tay-Sachs' disease and allied heredofamilial neurodegenerative disease of infancy and childhood. The scope of the program will include, in addition to Tay-Sachs' disease, Niemann-Pick's disease, infantile Gaucher's disease, Schilder's disease, diffuse sclerosis, amyotonia congenita, Friedreich's ataxia, and others. The foundation is known as National Tay-Sachs Association, Inc., New York Chapter, and is composed of parents who have had afflicted children, interested laymen, and medical personnel in the field.

The foundation is cooperating with the existing clinical and research program on Tay-Sachs' disease and certain of these allied diseases at Jewish Chronic Disease Hospital in Brooklyn. The hospital is presently conducting a special clinic for outpatient care of afflicted children and is constructing a special ward for the care and observation of inpatient cases. Both of these programs are being conducted in conjunction with the laboratory research program of the Isaac Albert Research Institute of the hospital. A comprehensive genetic study is also being made of the pertinent hereditary patterns from histories supplied by the foundation and parents who have children under the care of the hospital. A counseling program is also offered.

The operation of the foundation is on a nationwide basis, and contact is being made for establishment of chapters in other metropolitan areas, in addition to the allied Tay-Sachs Association in Philadelphia. In order to further its work and, in particular, to prepare a substantial genetic study covering the entire country, physicians and hospitals are respectfully requested to make the existence of the foundation known to parents of children afflicted with these diseases.

For further information on the foundation and its work, write to Medical Committee, National Tay-Sachs Association, Inc., New York Chapter, P. O. Box 1250, G. P. O., New York 1.

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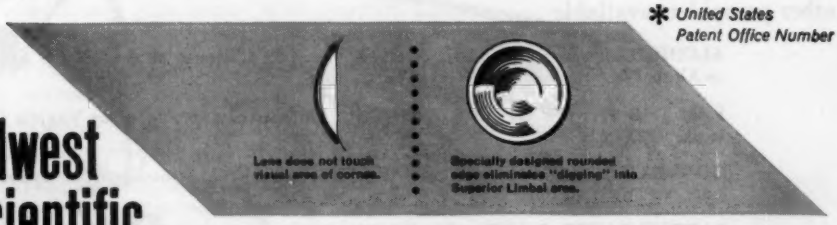
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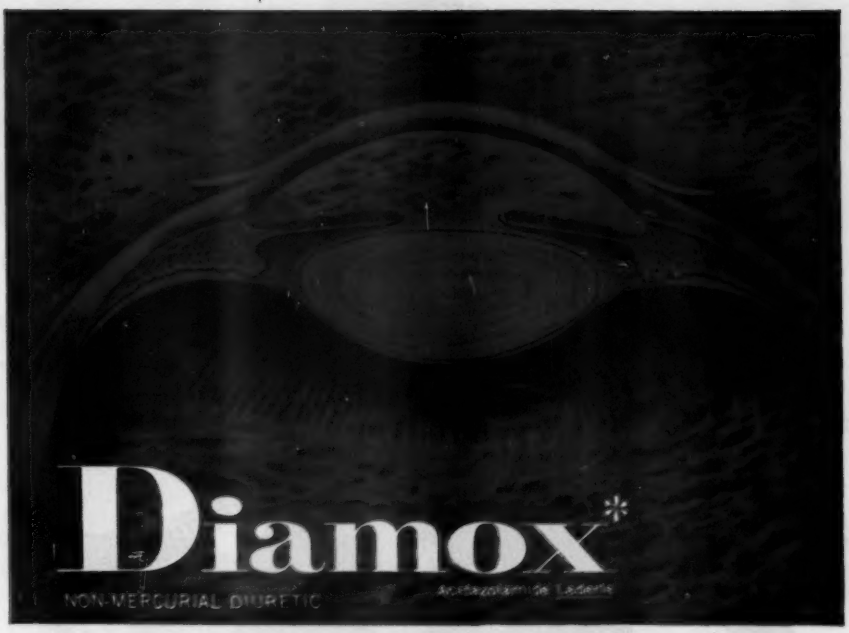

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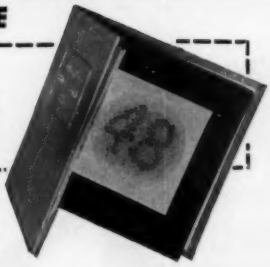

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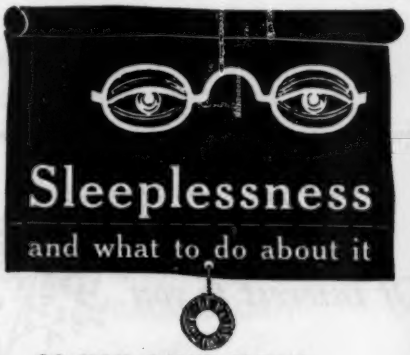

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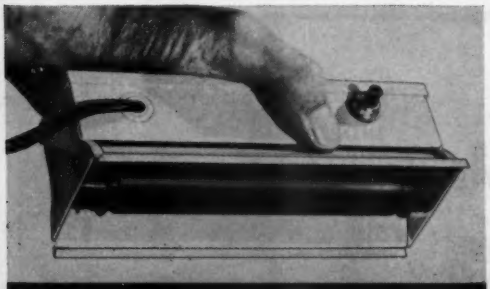

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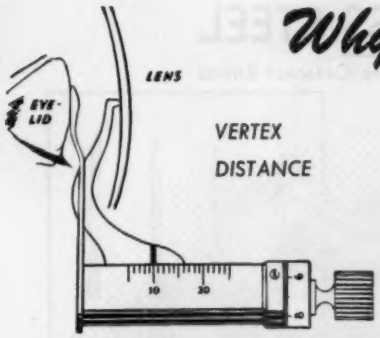

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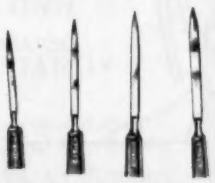

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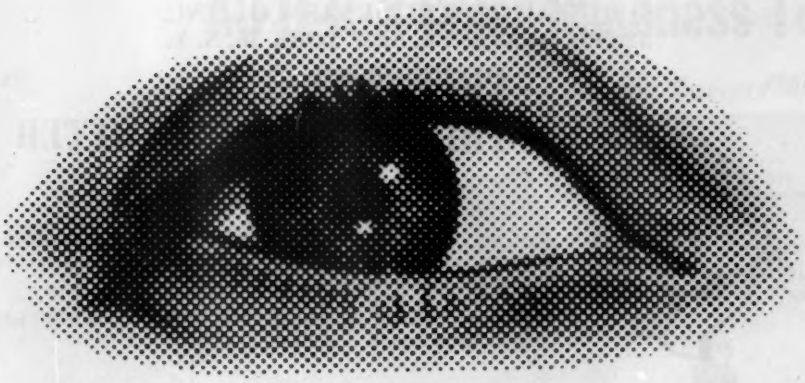

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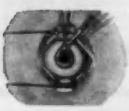

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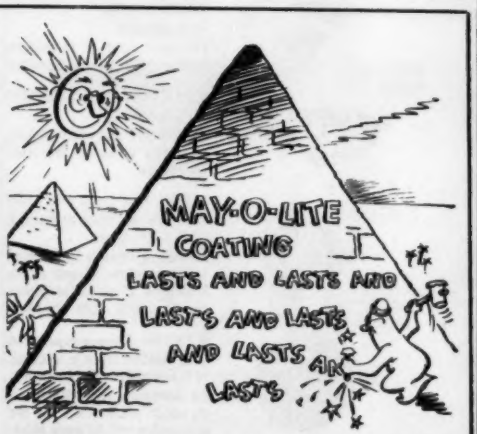

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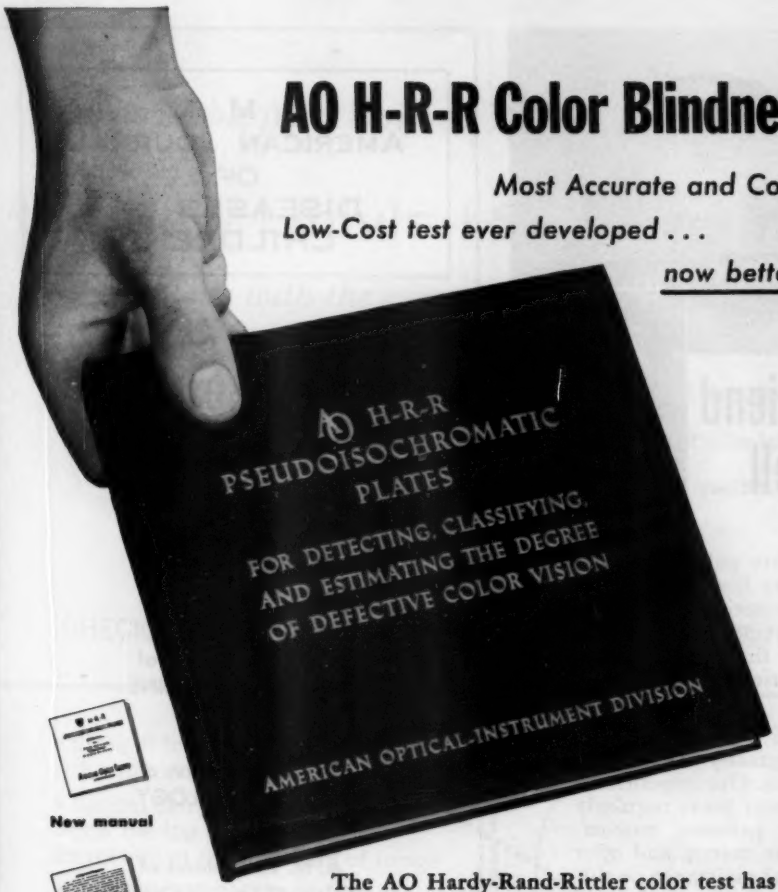

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New instructions

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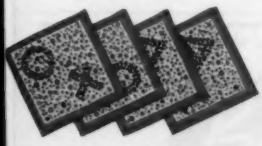

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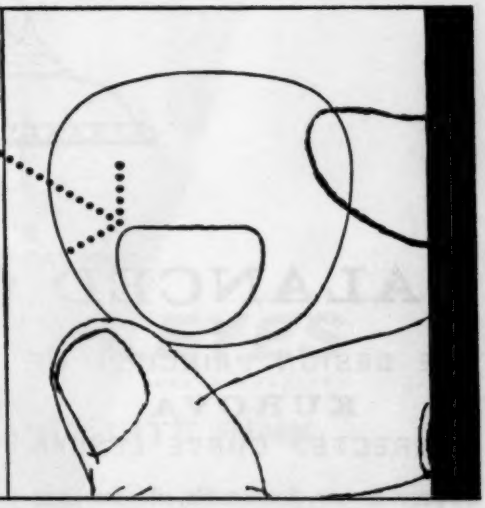

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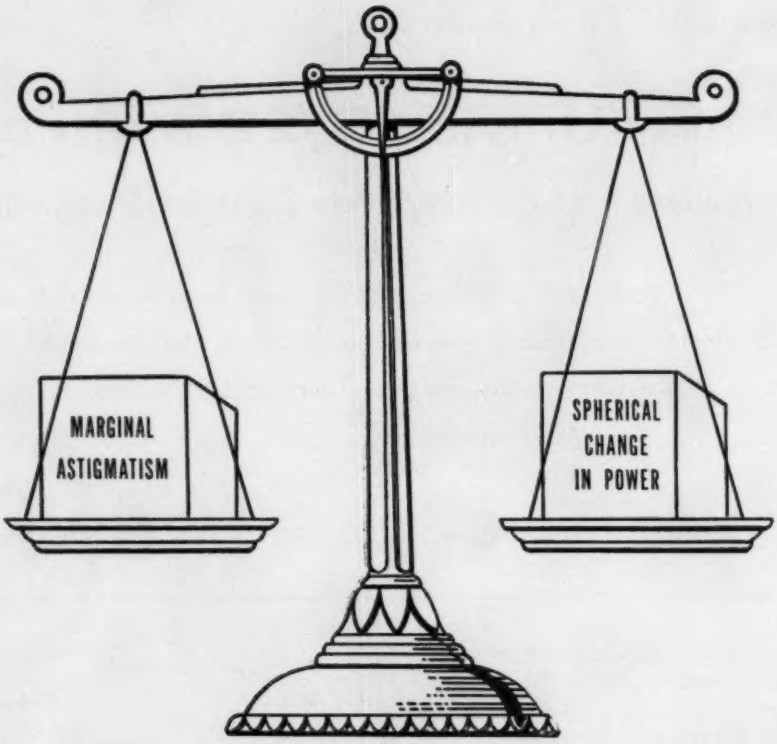

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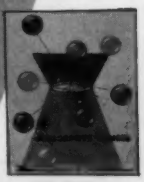

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